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(54) Title: METHOD FOR THE TREATMENT OF POLYCYSTIC KIDNEY DISEASE

(57) Abstract: The present invention provides a method for treating, inhibiting the progression of, or eradicating polycystic kidney disease of in a patient in need thereof which comprises providing to said patient an effective amount of a TACE inhibitor compound alone or in combination with an effective amount of an EGF receptor kinase inhibitor.

METHOD FOR THE TREATMENT OF POLYCYSTIC KIDNEY DISEASE

FIELD OF INVENTION

The present invention relates to a method of treating polycystic kidney disease. More particularly it involves the use of tumor necrosis factors-alpha converting enzyme (TACE) inhibitor, alone or in combination with other agent(s) such as EGF receptor kinase inhibitor, to treat the disease.

BACKGROUND

Autosomal recessive polycystic kidney disease (ARPKD) is an inherited disorder that usually presents in the newborn period with massive kidney enlargement (due to rapidly expanding cysts) and hepatic fibrosis. ARPKD occurs in approximately 1:10,000 to 1:40,000 births and produces significant morbidity and mortality. Data from experimental models of both recessive and dominant forms of PKD have identified three key pathophysiologic processes in cyst formation and enlargement: increased cell proliferation, increased fluid secretion and altered matrix biology. (Marcia NS, Sweeny WE Armer ED: New insights into the molecular pathophyscology of polycystic kidney disease, *Kidney Int.*, 55:1187-1197, 1999). A growing body of evidence has established the central role of the epidermal growth factor receptor (EGFR) in the pathogenesis of cell proliferation in PKD.

Published reports have also suggested that transforming growth factor-α (TGF-α) a ligand of the EGFR, is abnormally expressed in PKD. Mice transgenic for TGF-α develop renal cysts. TGF-α is present in mitogenic quantities in cyst fluid from *bpk* mice (a murine model of ARPKD) and immunoprecipitation of TGF-α reduces this mitogenic effect (Abstract; *J Am Soc Nephrol* 7:1610, 1996).

US Patent 6,002,008 discloses that certain EGF receptor kinase inhibitors are useful in the treatment of PKD; however no disclosure of the present invention is disclosed therein.

There is currently no completely effective therapy for polycystic kidney disease. A search for therapeutic agents useful for the treatment of PKD is ongoing.

SUMMARY OF INVENTION

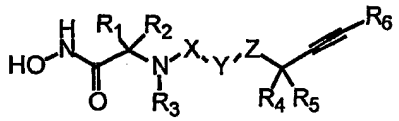
The present invention provides a method for treating, inhibiting the progression of, or eradicating polycystic kidney disease of in a patient in need thereof which comprises providing to said patient an effective amount of a TACE inhibitor compound alone or in combination with an effective amount of an EGF receptor kinase inhibitor.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a method for treating, inhibiting the progression of, or eradicating polycystic kidney disease of in a mammal in need thereof which comprises providing an effective amount of a TACE inhibitor compound.

Preferred TACE inhibitor compounds are described in WO 00/44730, WO 00/44749, WO 00/44709, WO 00/44711, WO 00/44710, WO 00/44716, WO 00/44740, WO 00/44713, and WO 00/44723 each of which is hereby incorporated by reference thereto.

Especially preferred TACE inhibitor compounds include those of formula I:



I

wherein:

X is SO_2 or -P(O)-R_{10};

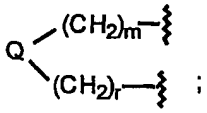
Y is aryl or heteroaryl, with the proviso that X and Z may not be bonded to adjacent atoms of Y;

Z is O, NH, CH_2 or S;

R_1 is hydrogen, aryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms;

R_2 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl of 3-6 carbon atoms, C_4-C_8 cycloheteroalkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms;

or R_1 and R_2, together with the atom to which they are attached, may form a ring wherein R_1 and R_2 represent a divalent moiety of the formula:



wherein

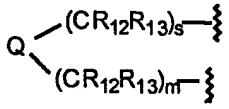
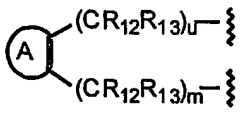
Q = a carbon-carbon single or double bond, O, S, SO, SO_2, -N-R_{11}, or -$CONR_{14}$;

m = 1-3;

r = 1 or 2, with the proviso that when Q is a bond, r is equal to 2;

R_3 is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, C4-C8 cycloheteroalkyl, aralkyl, or heteroaralkyl;

or R_1 and R_3, together with the atoms to which they are attached, may form a 5 to 8 membered ring wherein R_1 and R_3 represent divalent moieties of the formulae:

 ; and 

wherein Q and m are as defined above;

A is aryl or heteroaryl;

s is 0-3;

u is 1-4;

R_4 and R_5 are each, independently, hydrogen or alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_6 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C_5-C_8-cycloheteroalkyl;

R_8 and R_9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, aralkyl, heteroaryl, heteroaralkyl, or -C4-C8-cycloheteroalkyl;

R_{10} is alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl or heteroaryl;

R_{11} is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, $-S(O)_nR_8$, $-COOR_8$, $-CONR_8R_9$, $-SO_2NR_8R_9$ or $-COR_8$;

R_{12} and R_{13} are independently selected from H, $-OR_8$, $-NR_8R_9$, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, $-COOR_8$; $-CONR_8R_9$; or R_{12} and R_{13} together form a -C3-C6-cycloalkyl of 3-6 carbon atoms or a -C5-C8-cycloheteroalkyl ring; or R_{12} and R_{13}, together with the carbon to which they are attached, form a carbonyl group;

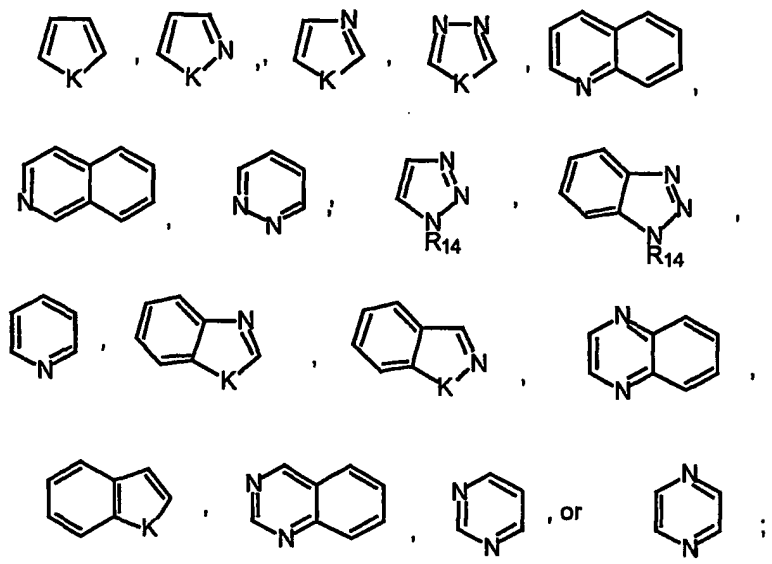
with the proviso that R_{10} and R_{12} or R_{11} and R_{12} may form a cycloheteroalkyl ring when they are attached to adjacent atoms;

R_{14} is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms or cycloalkyl of 3-6 carbon atoms;

and n is 0-2;

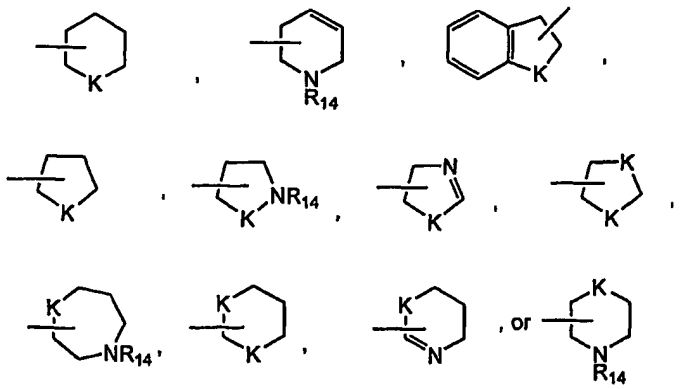
or a pharmaceutically acceptable salt thereof.

Heteroaryl, as used throughout, is a 5-10 membered mono- or bicyclic ring having from 1-3 heteroatoms selected from N, NR_{14}, S and O. Heteroaryl is preferably



wherein K is O, S or –NR14 and R14 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms. Preferred heteroaryl rings include pyrrole, furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, triazole, pyrazole, imidazole, isothiazole, thiazole, isoxazole, oxazole, indole, isoindole, benzofuran, benzothiophene, quinoline, isoquinoline, quinoxaline, quinazoline, benzotriazole, indazole, benzimidazole, benzothiazole, benzisoxazole, and benzoxazole. Heteroaryl groups may optionally be mono or di substituted.

C4-C8 cycloheteroalkyl as used herein refers to a 5 to 9 membered saturated or unsaturated mono or bi-cyclic ring having 1 or 2 heteroatoms selected from N, NR_{14}, S or O. Heterocycloalkyl rings of the present invention are preferably selected from;



wherein K is NR_{14}, O or S and R_{14} is a bond, hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms. Preferred heterocycloalkyl rings include piperidine, piperazine, morpholine, tetrahydropyran, tetrahydrofuran or pyrrolidine. Cycloheteroalkyl groups of the present invention may optionally be mono- or di- substituted.

Aryl, as used herein refers to a phenyl or napthyl rings which may, optionally be mono-, di- or tri-substituted.

Alkyl, alkenyl, alkynyl, and perfluoroalkyl include both straight chain as well as branched moieties. Alkyl, alkenyl, alkynyl, and cycloalkyl groups may be unsubstituted (carbons bonded to hydrogen, or other carbons in the chain or ring) or may be mono- or poly-substituted. Lower alkyl moieties contain from 1 to 6 carbon atoms.

Aralkyl as used herein refers to a substituted alkyl group, -alkyl-aryl, wherein alkyl is lower alkyl and preferably from 1 to 3 carbon atoms, and aryl is as previously defined.

Heteroaralkyl as used herein refers to a substituted alkyl group, alkyl-heteroaryl wherein alkyl is lower alkyl and preferably from 1 to 3 carbon atoms, and heteroaryl is as previously defined.

Halogen means bromine, chlorine, fluorine, and iodine.

Suitable substituents of aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl, alkenyl, alkynyl, and cycloalkyl include, but are not limited to hydrogen, halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms; alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, $-OR_8$, $-[[O(CH_2)_p]_q]$-OCH3, CN, $-COR_8$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms,$-CONR_8R_9$, $-S(O)_nR_8$, $-S(O)_nR_{18}C(O)OR_8$, $-S(O)_nR_{18}OR_9$, $-S(O)_nR_{18}NR_8R_9$, $-S(O)_nR_{18}NR_8R_9COOR_8$, $-S(O)nR_{18}NR_8COR_9$,- $OPO(OR_8)OR_9$, $-PO(OR_8)R_9$, $-OC(O)NR_8R_9$, $-C(O)NR_8OR_9$,- $C(O)R_{18}NR_8R_9$, $-COOR_8$, $-SO_3H$, $-NR_8R_9$, $-N[(CH_2)_2]_2NR_8$, $-NR_8COR_9$, - $NR_8C(O)CH=CHaryl$, $-NR_8C(O)(CH_2)_nNR_8R_9$, $-NR_8C(O)CH_2NHCH_2aryl$, $NR_8C(O)R_{18}$, $-NR_8COOR_9$, $-SO_2NR_8R_9$, $-NO_2$, $-N(R_8)SO_2R_9$, $-NR_8CONR_8R_9$, $-NR_8C(=NR_9)NR_8R_9$, $-NR_8C(=NR_9)N(SO2R_8)R_9$, $NR_8C(=NR_9)N(C=OR_8)R_9$ -tetrazol-5-yl, - SO_2NHCN, $-SO_2NHCONR_8R_9$, -(OR18)$NR_8S(O)R_9$, $-(OR_{18})NR_8C(O)R_9$, -

$(OR_{18})NR_8C(O)NR_8R_9$, -(OR18)NR_8COOR_9, -$(OR_{18})NR_8R_9$, phenyl, heteroaryl, or -C_4-C_8-cycloheteroalkyl;

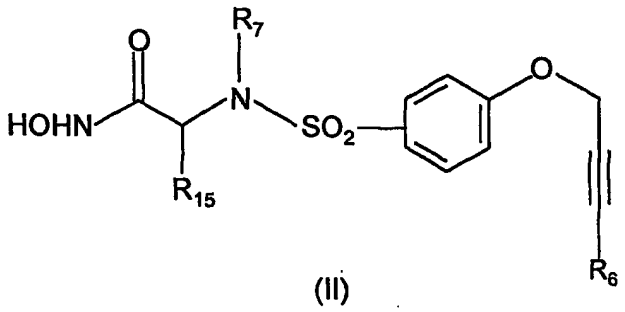
wherein -NR_8R_9 may form a heterocyclic group as previously defined, such as pyrrolidine, piperidine, morpholine, thiomorpholine, oxazolidine, thiazolidine, pyrazolidine, piperazine, and azetidine ring; p is 1 or 2, q is 1 through 3 and

R_{18} is alkyl of 1-20 carbon atoms.

In some preferred embodiments of the present invention R_8 and R_{18} may be further substituted with halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy and OH, and NO_2.

When a moiety contains more than substituent with the same designation (i.e., phenyl tri-substituted with R_1) each of those substituents (R_1 in this case) may be the same or different.

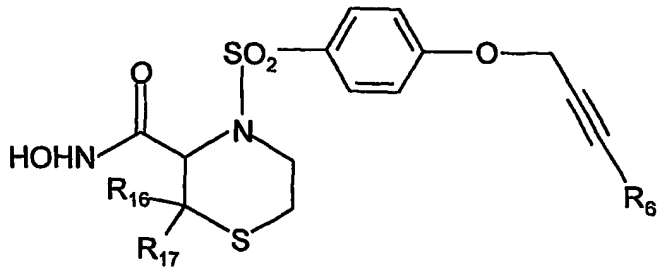
Especially preferred TACE inhibitor compounds of the present invention include compounds of formula II, III and IV:



(II)

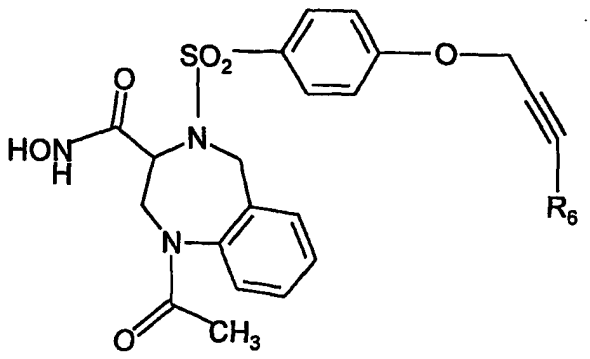
wherein

R_6 is as defined above with CH_3 and CH_2OH being preferred; R_7 is H or alkyl with H or methyl being preferred; and R_{15} is alkyl, with isopropyl and $CH(CH_3)OH$ being preferred.



(III)

wherein R_6 is defined as above with methyl and CH_2OH being preferred; R_{16} and R_{17} are alkyl preferably methyl.



(IV)

wherein R_6 is as defined above with methyl being preferred.

TACE inhibitor compounds which are especially useful in the present invention are 4-(4-but-2-ynyloxy-benzenesulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide; (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholinecarboxamide; (2R)-N-hydroxy-2-[({4-[(4-hydroxy-2-butynyl)oxy]phenyl}sulfonyl)(methyl)amino]-3-methylbutanamide; and (2R,3S)-2-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N,3-dihydroxybutanamide.

The present invention also encompasses a method for the treatment of PKD by using a TACE inhibitors compound in combination with an EGF receptor kinase inhibitor.

Preferred EGF receptor kinase inhibitor compounds are described in US Patent 6,002,008 which is hereby incorporated by reference thereto. The compound 4-dimethylamineo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide is especially preferred.

Preferred TACE inhibitor compounds of the present invention are described in WO 00/44730, WO 00/44749, WO 00/44709, WO 00/44711, WO 00/44710, WO 00/44716, WO 00/44740, WO 00/44713, and WO 00/44723. For example the following compounds are preferred compounds in the present invention: 4-(4-substituted-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-hydroxamic acids such as

1-Acetyl-4-(4-but-2-ynyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-But-2-ynyloxy-benzene-sulfonyl)-1-(2-thienylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

1-Benzoyl-4-(4-but-2-ynyloxybenzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(2-furanylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(methanesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-But-2-ynyloxybenzene-sulfonyl)-1-methoxyacetyl-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(3-pyridinylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(4-pyridinylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

1-Benzoyl-4-(4-[4-methoxybut-2-ynyloxy]benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-[4-Methoxybut-2-ynyloxy] benzenesulfonyl)-1-(3-pyridinylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-Pent-2-ynyloxy- benzene-sulfonyl)-1-(3-pyridinylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-[4-Hydroxybut-2-ynyloxy]benzenesulfonyl)-1-(4-pyridinylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzo-diazepine-3-carboxylic acid, hydroxyamide;

4-(4-[4-Methoxybut-2-ynyloxy]-benzenesulfonyl)-1-(2-thienylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

1-(Benzoyl)-4-(4-pent-2-ynyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

1-Propionyl-4-(4-[4-hydroxybut-2-ynyloxy]benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

1-(N,N-Dimethylaminoacetyl)-4-(4-[4-methoxybut-2-ynyloxy]benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
1-(Acetylaminoacetyl)-4-(4-but-2-ynyloxybenzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
1-(Ethoxyacetyl)-4-(4-[4-methoxybut-2-ynyloxy]benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzenesulfonyl)-1-(3-thienylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
1-(Ethoxyacetyl)-4-(4-[4-ethoxybut-2-ynyloxy]benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
1-(Acetylaminoacetyl)-4-(4-[4-methoxybut-2-ynyloxy]benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
1-(Cyclopropylcarbonyl)-4-(4-[4-methxybut-2-ynyloxy]benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
1-(Cyclobutylcarbonyl)-4-(4-but-2-ynyloxybenzeneulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(propionyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-[4-Methoxybut-2-ynyloxy]benzenesulfonyl)-1-(3-methyl-2-thienylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(3-methoxypropionyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(2-chlorobenzoyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(2-fluorobenzoyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(4-methyl-2-furanylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(3-furanylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(phenoxyacetyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;

4-(4-But-2-ynyloxybenzene-sulfonyl)-1-[2-(1-pyrazolyl)phenylcarbonyl]-7-methyl-2,3,4,5-tetrahydro-1H-[1,4]-benzodiazepene-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(5-chloro-2-thienylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(5-chloro-2-furanylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-[4-Methoxybut-2-ynyloxy]-benzenesulfonyl)-1-propionyl-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-[4-Methoxybut-2-ynyloxy]benzenesulfonyl)-1-(3-thienylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzo- diazepine-3-carboxylic acid, hydroxyamide;
1-(Aminoacetyl)-4-(4-but-2-ynyloxybenzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
1-Hexanoyl-4-(4-[4-methoxybut-2-ynyloxy]benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(N,N-Dimethylaminoacetyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzene-sulfonyl)-1-(cyclopropylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide;
4-(4-But-2-ynyloxybenzenesulfonyl)-1-(cycloyhexylcarbonyl)-2,3,4,5-tetrahydro-1H-[1,4]-benzodiazepine-3-carboxylic acid, hydroxyamide;
1-Methoxyacetyl-4-(4-[4-methoxybut-2-ynyloxy]benzenesulfonyl)-7-methyl-2,3,4,5-tetrahydro-1H-[1,4]-benzodiazepine-3-carboxylic acid, hydroxyamide;
1-Benzoyl-4-(4-but-2-ynyloxybenzenesulfonyl)-7-methyl-2,3,4,5-tetrahydro-1H-[1,4]-benzodiazepine-3-carboxylic acid, hydroxyamide;
1-(Benzoyl)-4-(4-but-2-ynyloxybenzenesulfonyl)-8-chloro-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid, hydroxyamide; and
1-Acetyl-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-7-fluoro-N-hydroxy-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-3-carboxamide.

Other preferred TACE inhibitor compounds include acetylenic ortho-sulfonamido and phosphinic acid amido bicyclic heteroaryl hydroxamic acids such as
4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid hydroxyamide;

4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-3-methyl-isoxazolo[5,4-b]pyridine-5-carboxylic acid hydroxyamide;

4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-8-methoxy-quinoline-3-carboxylic acid hydroxyamide;

4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-3-methyl-isothiazolo[5,4-b]pyridine-5-carboxylic acid hydroxyamide; and

8-Bromo-4-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino]-N-hydroxy-3-quinolinecarboxamide.

Still other preferred TACE inhibitor compounds include aryl sulfonamide hydroxamic acid MMP/TACE inhibitors in which the sulfonyl aryl group is para-substituted with a substituted butynyl moiety or a propargylic ether, amine or sulfide such as

2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-butyramide;

2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-acetamide

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-butyramide;

2-[(4-But-2-ynyloxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-acetamide hydrochloride;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-acetamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-3-methyl-butyramide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-propionamide;

2-[(4-But-2-ynyloxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-propionamide hydrochloride;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-2-methyl-propionamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

4-(4-Hept-2-ynyloxy-benzenesulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

2-(4-But-2-ynyloxy-benzenesulfonyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid hydroxyamide;

4-Benzoyl-1-(4-but-2-ynyloxy-benzenesulfonyl)-[1,4]diazepane-2-carboxylic acid hydroxyamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-4-methyl-piperazine-2-carboxylic acid hydroxyamide hydrochloride;

4-[4-(4-Hydroxy-but-2-ynyloxy)-benzenesulfonyl]-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-3-hydroxycarbamoyl-piperazine-1-carboxylic acid tert-butyl ester;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-2-methylpropionamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-5-guanidino-pentanoic acid hydroxyamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-5-(4-methylbenzenesulfonyl-guanidino)-pentanoic acid hydroxyamide;

3-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-succinamic acid cyclohexyl ester;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-3-cyclohexyl-N-hydroxy-propionamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-2-cyclohexyl-N-hydroxy-acetamide

3-tert-Butylsulfanyl-2-(4-but-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-propionamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-3-(4-methoxy-benzylsulfanyl)-propionamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N1-hydroxy-succinamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-3-cyclohexyl-N-hydroxy-propionamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-2-cyclohexyl-N-hydroxy-acetamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-4-methyl-pentanoic acid hydroxyamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-4-methylsulfanyl-butyramide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-3-phenyl-propionamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid hydroxyamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-3-(1H-indol-3-yl)-propionamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-3-(4-hydroxy-phenyl)-propionamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-3-methyl-butyramide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-4-methyl-pentanoic acid hydroxyamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-6-(2-chloro-benzylamino)-hexanoic acid hydroxyamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-hexanoic acid hydroxyamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-2-phenyl-acetamide;

3-Benzyloxy-2-(4-but-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-propionamide;

2-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-acetamide;

(2R,3S)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-methyl pentanamide;
(2R)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3,3-dimethyl-butanamide;
(2S)-2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-propionamide;
2-[(4-But-2-ynyloxy-benzenesulfonyl)-ethyl-amino]-N-hydroxy-3-methyl-butyramide;
2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(2-propynyl)amino]-N-hydroxy-3- methylbutanamide;
2-[(4-But-2-ynyloxy-benzenesulfonyl)-propyl-amino]-N-hydroxy-3-methyl-butyramide;
2-[(4-But-2-ynyloxy-benzenesulfonyl)-(3-phenyl-propyl)-amino]-N-hydroxy-3-methyl-butyramide;
2-[(4-But-2-ynyloxy-benzenesulfonyl)-cyclopropylmethyl-amino]-N-hydroxy-3-methyl-butyramide;
2-[(4-But-2-ynyloxy-benzenesulfonyl)-isobutyl-amino]-N-hydroxy-3-methyl-butyramide;
2-[(4-But-2-ynyloxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-butyramide;
2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-2-cyclohexyl-N-hydroxy-acetamide;
2-[(4-But-2-ynyloxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-2-cyclohexyl-N-hydroxy acetamide;
2-{(4-But-2-ynyloxy-benzenesulfonyl)-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-amino}-2-cyclohexyl-N-hydroxy-acetamide;
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[3-(diethylamino)propyl]amino}-N-hydroxy-3-methylbutanamide;
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[3-(4-morpholinyl)propyl]amino}-N-hydroxy-3-methylbutanamide;
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[3-(4-methyl-1-piperazinyl)propyl]-amino}-N-hydroxy-3-methylbutanamide hydrochloride;
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[4-(diethylamino)butyl]amino}-N-hydroxy-3-methylbutanamide;
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[4-(4-methyl-1-piperazinyl)butyl]amino}-N-hydroxy-3-methylbutanamide;
2-[[[4-(2-Butynyloxy)phenyl]sulfonyl][2-(4-morpholinyl)ethyl]amino]-N-hydroxy-3-methylbutanamide;
2-[{[4-(But-2-ynyloxy)phenyl]sulfonyl}(2-morpholin-4-ylethyl)amino]-N-hydroxyacetamide hydrochloride;

2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[4-(4-methyl-1-piperazinyl)-2-butynyl]amino}-N-hydroxy-3-methylbutanamide;

2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[4-(diethylamino)-2-butynyl]amino}-N-hydroxy-3-methylbutanamide;

2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[4-(methylamino)-2-butynyl]amino}-N-hydroxy-3-methylbutanamide;

((2R)-{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino)[(4-diethylamino)-cyclohexyl]–N-hydroxyethamide;

(2R)-{[4-(2-Butynyloxy)phenyl]sulfonyl}amino-N-hydroxy–2-(4-hydroxycyclo-hexyl)ethanamide;

(2R)-{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino)-N-hydroxy–2-(4-hydroxycyclohexyl)-ethanamide;

2-[(6-But-2-ynyloxy-pyridine-3-sulfonyl)-methyl-amino]-N-hydroxy-acetamide;

2-[[(4-{[3-(4-Chlorophenyl)-2-propynyl]oxy}phenyl)sulfonyl](methyl)amino]-N-hydroxyacetamide;

N-Hydroxy-2-(methyl{[4-(prop-2-ynylamino)phenyl]sulfonyl}amino)acetamide;

2-[(4-But-2-ynylthiophenylsulfonyl)methylamino]-N-hydroxyacetamide;

2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[4-(4-methyl-1-piperazinyl)-2-yl}[4-(4-methyl-1-piperazinyl)-2-butynyl]amino}-N-hydroxypropanamide;

1-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-sulfonyl}(methyl)-amino]-N-hydroxycyclohexanecarboxamide;

1-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(3-pyridinylmethyl)amino]N-hydroxy-cyclohexanecarboxamide;

1-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexane-carboxamide;

1-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclopentane-carboxamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl)(methyl)amino]–N-hydroxy–3-methyl-3-[(2-(4-morpholinylethyl)sulfanyl]–butanamide hydrochloride;

2-({[4-(2-Butynyloxy)phenyl] sulfonyl)(methyl)amino]–N-hydroxy–3-methyl-3-{[2-(4-methyl-1-ethyl-1-piperazinyl)ethyl]sulfanyl}butanamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl)(methyl)amino]–N-hydroxy–3-methyl-3-{[2-(diethylamino)ethyl]sulfanyl}butanamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl)(methyl)amino]–N-hydroxy–3-methyl-3-{[2-(1-pyrrolidinyl)ethyl]sulfanyl}butanamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl)(methyl)amino]–N-hydroxy–3-methyl-3-{[2-(1H-imidazol-1-yl)ethyl]sulfanyl}butanamide;

Methyl 1-[2-({2-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)]amino]–3-(hydroxyamino)-1,1-dimethyl-3-oxopropyl}sulfanyl)ethyl]-2–pyrrolidine-carboxylate;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl)(methyl)amino]–N-hydroxy–3-methyl-3-[(2(4-morpholinylpropyl)sulfanyl]–butanamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl)(methyl)amino]–N-hydroxy–3-methyl-3-{[2(4-methyl-1-ethyl-1-piperazinyl)propyl]sulfanyl}butanamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl)(methyl)amino]–N-hydroxy–3-methyl-3-{[2-(diethylamino)propyl]sulfanyl}butanamide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-3-methylsulfanyl-butyramide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-3-ethylsulfanyl-butyramide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-3-propylsulfanyl-butyramide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-3-(pyridin-3-ylmethylsulfanyl)-butyramide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-3-benzylsulfanyl-butyramide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-methyl-amino]-N-hydroxy-3-(methylsulfanyl)-butyramide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-methyl-amino]-N-hydroxy-3-(pyridin-3-ylmethylsulfanyl)-butyramide;

3-(Benzylthio)–2-[[[4-(2-butynyloxy)phenyl]sulfonyl]methylamino]-N-hydroxy-propanamide;

3-(Benzylthio)–2-[[[4-(2-butynyloxy)phenyl]sulfonyl]pyridin-3-ylmethylamino]–N-hydroxypropanamide;

2-[[[4-(2-Butynyloxy-phenyl]sulfonyl]amino]-N-hydroxy-3-methyl-(3-methylthio)-butyramide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-amino]-N-hydroxy-3-methyl-3-ethylsulfanyl-butyramide;

2-[(4-But-2-ynyloxy-benenesulfonyl)-amino]-N-hydroxy-3-methyl-3-propylsulfanyl-butyramide;

2-[(4-Butynyloxy-phenylsulfonyl)-amino]-N–hydroxy-3–methyl-[(3-pyridinyl-methyl)thio] butyramide;

2-[(4-Butynyloxy-phenyl)sulfonyl)-amino]-N-hydroxy-3-methyl-(3-benzyl-sulfanyl) butyramide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino–N-hydroxy–3-{[(-methyl–1H-imidazol–2–yl]methylsulfanyl}butanamide;

2-({[4-(2-butynyloxy)phenyl]sulfonyl}amino–N-hydroxy–3-methyl-3–{[2–(4–morpholinyl) ethyl]sulfanyl}butanamide;

tert-Butyl{[2-({[4-2-butynyloxy)phenyl]sulfonyl}amino)–3-(hydroxyamino)–1,1-dimethyl-3-oxopropyl]sulfanyl}acetate;

tert-Butyl {[2-({[4-2-butynyloxy)phenyl]sulfonyl}amino)–3-(hydroxyamino)–1,1-dimethyl – 3-oxopropyl]sulfanyl acetic acid, sodium salt;

2-[(4–Butynyloxy-phenylsulfonyl)–amino]-N-hydroxy-3-(methylthio)-propanamide;

2-[[4–Butynyloxy-phenylsulfonyl]–amino]-N-hydroxy-3-(benzylthio)-propanamide;

2-[[4–Butynyloxy-phenylsulfonyl]–amino]-N-hydroxy-3-(pyridinylthio)-propanamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-[(Z)-11-tetradecenylsulfanyl]propanamide;

(2S)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-[(3-hydroxy-propyl)sulfanyl]-3-methylbutanamide;

(2S)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-[(3-hydroxy-propyl)sulfanyl]-3-propanamide;

(3S)-4-({[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-1,4-thiazepane-3-carboxamide;

(3S)-4-({[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-1,4-thiazepane-3-carboxamide;

(3S)-4-({[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-1,4-thiazepane-3-carboxamide 1,1-dioxide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-(4-hydroxy-phenyl)acetamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-[4-(2-propynyloxy)-phenyl]acetamide;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-2-(4-methoxyphenyl)acetamide;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-2-{4-[2-(4-morpholinyl)ethoxy]phenyl}acetamide;

tert-Butyl 2-{4-[1-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]-2-(hydroxyamino)-2-oxoethyl]phenoxy}ethylcarbamate;

2-[4-(2-Aminoethoxy)phenyl]-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}-(methyl)amino]-N-hydroxyacetamide;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-2-{4-[2-(dimethylamino)-ethoxy]phenyl}-N-hydroxyacetamide;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-2-{4-[2-(1-pyrrolidinyl)ethoxy]phenyl}acetamide;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-2-{4-[2-(2-oxo-1-pyrrolidinyl)ethoxy]phenyl}acetamide;

tert-Butyl 4-(2-{4-[1-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]-2-(hydroxyamino)-2-oxoethyl]phenoxy}ethyl)-1-piperazinecarboxylate;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-2-{4-[2-(1-piperazinyl)ethoxy]phenyl}acetamide;

tert-Butyl 3-{4-[1-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]-2-(hydroxyamino)-2-oxoethyl]phenoxy}propylcarbamate;

2-[4-(3-Aminopropoxy)phenyl]-2-[{[4-(2-butynyloxy)phenyl]-sulfonyl}(methyl)amino]-N-hydroxyacetamide;

tert-Butyl (3S)-3-{4-[(1R)-1-[{[4-(2-butynyloxy)phenyl]sulfonyl}-(methyl)amino]-2-(hydroxyamino)-2-oxoethyl]phenoxy}-1-pyrrolidine-carboxylate;

(2R)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-2-{4-[(3S)-pyrrolidinyloxy]phenyl}ethanamide;

tert-Butyl (2-{4-[1-({[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino)-2-(hydroxyamino)- 2-oxoethyl)phenoxy]ethyl)–(methyl)carbamate;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino)-N-hydroxy-2-{4-[2-(methylamino) ethoxy]phenyl}acetamide;

Ethyl 3-{4-[1-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]-2-(hydroxyamino)-2-oxoethyl]phenoxy}propylcarbamate;

2-{4-[3-(Acetylamino)propoxy]phenyl}-2-[{[4-(2-butynyloxy)phenyl]-sulfonyl}(methyl)amino]-N-hydroxyacetamide;

Butyl-3-{4-[1-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]-2-(hydroxyamino)-2-oxoethyl]phenoxy}propylcarbamate;

Benzyl-3-{4-[1-[{[4-(2-butynyloxy)phenyl]sulfonyl}(methyl)amino]-2-(hydroxyamino)-2-oxoethyl]phenoxy}propylcarbamate;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-2-(4-{3-[(methylsulfonyl)amino]propoxy}phenyl)acetamide;

2-(4-{3-[(Anilinocarbonyl)amino]propoxy}phenyl)-2-[{[4-(2-butynyloxy)-phenyl]sulfonyl}(methyl)amino]-N-hydroxyacetamide;

tert-Butyl 2-{4-[(1R)-1-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-2-(hydroxyamino)-2-oxoethyl]phenoxy}ethylcarbamate;

(2R)-2-[4-(2-Aminoethoxy)phenyl]-2-({[4-(2-butynyloxy)phenyl]-sulfonyl}-amino)-N-hydroxyethanamide;

(2R)-2-{4-[2-(Acetylamino)ethoxy]phenyl}-2-({[4-(2-butynyloxy)phenyl]-sulfonyl}amino)-N-hydroxyethanamide;

tert-Butyl 4-(2-{4-[1-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-2-(hydroxyamino)-2 -oxoethyl)phenoxy]ethyl)–1-piperazinecarboxylate;

tert-Butyl 4-(2-{4-[1-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-2-(hydroxyamino)-2-oxoethyl)phenoxy]ethyl)–(methyl)carbamate;

2-{[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-{4-[2-(methylamino)ethoxy]phenyl})acetamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-{4-[2-(1-pyrrolidinyl)ethoxy]phenyl}acetamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-{4-[2-(4-morpholinyl)ethoxy]phenyl}acetamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino){4-[2-(dimethylamino)ethoxy]-phenyl}-N-hydroxyacetamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-{4-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]phenyl}acetamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-(4-{2-[2-(2-thoxyethoxy)ethoxy]ethoxy}phenyl)acetamide;

2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-{4-[2-(2-methoxy-ethoxy)ethoxy]phenyl}acetamide;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxy-2-phenyl-acetamide;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-2-(4-chlorophenyl)-N-hydroxyacetamide;

2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-5-[(4-chlorophenyl)-sulfanyl]-N-hydroxypentanamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-piperazine-2-carboxylic acid hydroxyamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-4-(morpholine-4-carbonyl)-piperazine-2-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-piperazine-1,3-dicarboxylic acid 1-diethylamide 3-hydroxyamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-4-(pyrrolidine-1-carbonyl)-piperazine-2-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-piperazine-1,3-dicarboxylic acid 1-diisopropylamide 3-hydroxyamide;

Benzyl 4-{[4-(2-butynyloxy)phenyl]sulfonyl}-3-[(hydroxyamino)carbonyl]-1-piperazinecarboxylate;

4-(4-But-2-ynyloxy-benzenesulfonyl)-piperazine-1,3-dicarboxylic acid 3-hydroxyamide 1-(methyl-phenyl-amide);

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-3-hydroxy-N-1-(4-methoxyphenyl)-1,3-piperazinedicarboxamide;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-1-(4-fluorophenyl)-N-3-hydroxy-1,3-piperazinedicarboxamide;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-1-(3,5-dichlorophenyl)-N-3-hydroxy-1,3-piperazinedicarboxamide;

4-Acetyl-1-(4-but-2-ynyloxy-benzenesulfonyl)-piperazine-2-carboxylic acid hydroxyamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-4-propionyl-piperazine-2-carboxylic acid hydroxyamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-4-(thiophene-2-carbonyl)-piperazine-2-carboxylic acid hydroxyamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-4-methanesulfonyl-piperazine-2-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-3-hydroxycarbamoyl-piperazine-1-carboxylic acid methyl ester;

{2-[4-(4-But-2-ynyloxy-benzenesulfonyl)-3-hydroxycarbamoyl-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid *tert*-butyl ester;

4-Aminoacetyl-1-(4-but-2-ynyloxy-benzenesulfonyl)-piperazine-2-carboxylic acid hydroxyamide;

1-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-[(2,2,5-trimethyl-1,3-dioxan-5-yl)carbonyl]-2-piperazinecarboxamide;

1-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoyl-2-piperazinecarboxamide;

4-(4-Bromo-benzyl)-1-(4-but-2-ynyloxy-benzenesulfonyl)-piperazine-2-carboxylic acid hydroxyamide;

1-(4-But-2-ynyloxy-benzenesulfonyl)-4-pyridin-3-ylmethyl-piperazine-2-carboxylic acid hydroxyamide;

(3S)–4-({[4-(2-Butynyloxy)phenyl]sulfonyl)–2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

9-({[4-(2-Butynyloxy)phenyl]sulfonyl}–N–hydroxy-6-thia-9-azaspiro[4,5]-decane-10-carboxamide;

9-({[4-(2-Butynyloxy)phenyl]sulfonyl}–N-hydroxy-1-thia-4-azaspiro[5,5]-undecane-5-carboxamide;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl)–2,2-diethyl-thiomorpholine-3-carboxylic acid hydroxyamide;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl)–N-hydroxy-thiomorpholine-3-carboxamide;

4-([4-(2-Butynyloxy)phenyl]sulfonyl}–N-hydroxy-3-morpholinecarboxamide;

9-Benzyl-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-thia-4,9-diazaspiro[5.5]undecane-5-carboxamide;

9-Methyl-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-thia-4,9-diazaspiro[5.5]undecane-5-carboxamide;

N-Hydroxy-2,2-dimethyl-4-[(4-{[5-(tetrahydro-2H-pyran-2-yloxy)-2-pentynyl]oxy}phenyl)sulfonyl]-3-thiomorpholine carboxamide;

N-Hydroxy-4-({4-[(5-hydroxy-2-pentynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide;

tert-Butyl 5-[4-({3-[(hydroxyamino)carbonyl]-2,2-dimethyl-4-thiomorpholinyl}sulfonyl)phenoxy]-3-pentynylcarbamate;

4-({4-[(5-Amino-2-pentynyl)oxy]phenyl}sulfonyl)-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide;

4-[(4-{[4-(Benzyloxy)-2-butynyl]oxy}phenyl)sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide;

N-Hydroxy-2,2-dimethyl-4-[(4-{[6-(tetrahydro-2H-pyran-2-yloxy)-2-hexynyl]-oxy}phenyl)sulfonyl]-3-thiomorpholine carboxamide;

N-Hydroxy-4-({4-[(6-hydroxy-2-hexynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide;

tert-Butyl 6-[4-({(3S)-3-[(hydroxyamino)carbonyl]-2,2- dimethyl-thiomorpholinyl}sulfonyl)phenoxy]-4-hexynylcarbamate;

(3S)-4-({4-[(6-Amino-2-hexynyl)oxy]phenyl}sulfonyl)-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide;

tert-Butyl 7-[4-({(3S)-3-[(hydroxyamino)carbonyl]-2,2- dimethyl-thiomorpholinyl}sulfonyl)phenoxy]-5-heptynylcarbamate;

(3S)-4-({4-[(7-Amino-2-heptynyl)oxy]phenyl}sulfonyl)-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide;

(3S)-N-Hydroxy-2,2-dimethyl-4-({4-[(3-phenyl-2-propynyl)oxy]-phenyl}sulfonyl)-3-thiomorpholine carboxamide;

(3S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide (1S)-oxide;

(3S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide (1R)-oxide;

(3S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide 1,1-dioxide;

(3S)-N-Hydroxy-2,2-dimethyl-4-{[4-(2-propynyloxy)phenyl]sulfonyl}-3-thiomorpholine carboxamide;

(3S)-N-Hydroxy-2,2-dimethyl-4-{[4-(2-pentynyloxy)phenyl]sulfonyl}-3-thiomorpholine carboxamide;

(3S)-N-Hydroxy-4-({4-[(4-hydroxy-2-butynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide;

4-[4-(((3S)-3-[(Hydroxyamino)carbonyl]-2,2-dimethylthiomorpholinyl}-sulfonyl)phenoxy]-2-butynyl acetate;

(3S)-N-Hydroxy-4-({4-[(6-hydroxy-2,4-hexadiynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholine carboxamide;

(3S)-N-Hydroxy-2,2-dimethyl-4-{[4-(2,4-pentadiynyloxy)phenyl]sulfonyl}-3-thiomorpholine carboxamide;

(3S)-4-({4-[(4-Fluoro-2-butynyl)oxy]phenyl}sulfonyl)-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide;

4-({4-[(4-Amino-2-butynyl)oxy]phenyl}sulfonyl)-N-hydroxy-2,2-dimethyl-3-thiomorpholine carboxamide;

tert-Butyl 4-[4-({3-[(hydroxyamino)carbonyl]-2,2-dimethyl-4-thiomorpholinyl}-sulfonyl)phenoxy]-2-butynylcarbamate;

tert-Butyl 4-[4-({3-[(hydroxyamino)carbonyl]-2,2-dimethyl-4-thiomorpholinyl}-sulfonyl)phenoxy]-2-butynyl(methyl)carbamate;

7-[4-(((3S)-3-[(Hydroxyamino)carbonyl]-2,2-dimethylthiomorpholinyl}-sulfonyl)phenoxy]-5-heptynyl acetate;

(3S)-N-Hydroxy-4-({4-[(7-hydroxy-2-heptynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholinecarboxamide;

(3S,5S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2,5-trimethyl-3-thiomorpholinecarboxamide;

(3S,5R)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2,5-trimethyl-3-thiomorpholinecarboxamide;

(3S,6S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2,6-trimethyl-3-thiomorpholinecarboxamide;

tert-Butyl{(2R,5S)-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-5-[(hydroxyamino)-carbonyl]-6,6-dimethylthiomorpholinyl}methylcarbamate;

tert-Butyl{(2S,5S)-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-5-[(hydroxyamino)-carbonyl]-6,6-dimethylthiomorpholinyl}methylcarbamate;

(3S,6R)-Trans-6-(aminomethyl)-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide hydrochloride;

(3S,6S)-Cis-6-(aminomethyl)-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide hydrochloride;

tert-Butyl{(2S,5S)-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-5-[(hydroxyamino)-carbonyl]-6,6-dimethylthiomorpholinyl}acetate;

{(2S,5S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-5-[(hydroxyamino)carbonyl]-6,6-dimethylthiomorpholinyl}acetic acid;

(3S,6S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-6-[2-(hydroxyamino)-2-oxoethyl]-2,2-dimethyl-3-thiomorpholinecarboxamide;

(3S,6S)-6-(2-Amino-2-oxoethyl)-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;

(3S,6S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-6-[2-(dimethylamino)-2-oxoethyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;

(3S,6S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-6-[2-(4-morpholinyl)-2-oxoethyl]-3-thiomorpholinecarboxamide;

(3S,6S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-6-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-3-thiomorpholinecarboxamide hydrochloride;

(3S,6S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-6-(2-{[2-(dimethylamino)-ethyl]amino}-2-oxoethyl)-N-hydroxy-2,2-dimethyl-3-thiomorpholine-carboxamide;

Methyl (3S,6S)-6-{[(*tert*-butoxycarbonyl)amino]methyl}-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-2,2-dimethyl-3-thiomorpholinecarboxylate;

(4S)-3-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-5,5-dimethyl-1,3-thiazolidine-4-carboxamide;

tert-Butyl 4-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxylate;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-4-piperidine-carboxamide;

1-Benzoyl-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1,4-diazepane-5-carboxamide;

1-Benzyl-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1,4-diazepane-5-carboxamide;

tert-Butyl 4-{[4-(2-butynyloxy)phenyl]sulfonyl}-5-[(hydroxyamino)carbonyl]-1,4-diazepane-1-carboxylate;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-1,4-diazepane-5-carboxamide;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-methyl-1,4-diazepane-5-carboxamide;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-1,4-thiazepine-5-carboxamide;

(2R)-5-(Acetylamino)-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypentanamide;

N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]thiophene-2-carboxamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-{[(ethylamino)carbonyl]-amino}-N-hydroxypentanamide;

(2R)-5-[(Anilinocarbonyl)amino]-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}-amino)-N-hydroxypentanamide;

Octyl (4R)-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentylcarbamate;

4-Methoxyphenyl (4R)-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentylcarbamate;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-{[(diethylamino)-carbonyl]amino}-N-hydroxypentanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-{[(methylanilino)carbonyl]amino}pentanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-{[(1-methyl-1H-imidazol-4-yl)sulfonyl]amino}pentanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-[(2-morpholin-4-ylacetyl)amino]pentanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-{[2-(4-methylpiperazin-1-yl)acetyl]amino}pentanamide;

(2R)-5-{[2-(Benzylamino)acetyl]amino}-2-({[4-(but-2-ynyloxy)phenyl]-sulfonyl}amino)-N-hydroxypentanamide;

(3S)-4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2,2-dimethyl-3,4-dihydro-2H-1,4-thiazine-3-carboxamide;

(2R)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-[(imino{[(4-{[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]amino}methyl)amino]pentanamide;

(2R)-2-(4-But-2-ynyloxy-benzenesulfonylamino)-5-guanidino-pentanoic acid hydroxyamide;

(2R)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-[(imino{[(4-methylphenyl)sulfonyl]amino}methyl)amino]pentanamide;

(3R)-3-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-4-(hydroxyamino)-4-oxobutanoic acid;
(2S)-3-(*tert*-Butylthio)-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide;
(2S)-3-{[(Acetylamino)methyl]thio}-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide;
(2S)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-[(4-methylbenzyl)thio]propanamide;
(2S)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-[(4-methoxybenzyl)thio]propanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypentanediamide;
(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentanoic acid;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-4-phenyl-butanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-(1H-imidazol-5-yl)propanamide;
(2R,4S)-1-{[4-(But-2-ynyloxy)phenyl]sulfonyl}-N,4-dihydroxypyrrolidine-2-carboxamide;
(2R)-6-Amino-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-hexanamide;
Benzyl (5R)-5-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexylcarbamate;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-(1-naphthyl)-propanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-(2-naphthyl)-propanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxyhexanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypentanamide;
(2R)-5-Amino-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypentanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-3-(3,4-difluorophenyl)-N-hydroxypropanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-3-(4-fluorophenyl)-N-hydroxypropanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-(4-nitrophenyl)-propanamide;
(2R)-1-{[4-(But-2-ynyloxy)phenyl]sulfonyl}-N-hydroxypiperidine-2-carboxamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N,3-dihydroxypropanamide;
(2R)-3-(Benzyloxy)-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-propanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-3-thien-2-yl-propanamide;
(2R,3S)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N,3-dihydroxybutanamide;
(2R,3S)-3-(Benzyloxy)-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxybutanamide;
(4S)-3-{[4-(But-2-ynyloxy)phenyl]sulfonyl}-N-hydroxy-1,3-thiazolidine-4-carboxamide;
(3R)-2-{[4-(But-2-ynyloxy)phenyl]sulfonyl}-N-hydroxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxamide;
(2R)-3-[4-(Benzyloxy)phenyl]-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-2-phenyl-ethanamide;
(2R)-5-(Acetylamino)-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-pentanamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]-1H-benzimidazole-5-carboxamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]benzamide;
4-Bromo-N-[(4R)-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxy-amino)-5-oxopentyl]benzamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(butyrylamino)-N-hydroxypentanamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]-3-chlorothiophene-2-carboxamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]-4-chlorobenzamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]cyclohexanecarboxamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-{[2-(3,4-dichlorophenyl)-acetyl]amino}-N-hydroxypentanamide;

N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]-2,5-dimethyl-3-furamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]-3,5-dimethylisoxazole-4-carboxamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-[(3-phenylpropanoyl)amino]pentanamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]isonicotinamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]nicotinamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]-2-methoxybenzamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]-4-methoxybenzamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-{[2-(4-nitrophenyl)acetyl]amino}pentanamide;
(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-[(2-phenylacetyl)amino]pentanamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]quinoline-3-carboxamide;
N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]thiophene-3-carboxamide;
(E)-N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]-3-phenylprop-2-enamide;
N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]-1H-benzimidazole-5-carboxamide;
N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]benzamide;
4-Bromo-N-[(5R)-5-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxy-amino)-6-oxohexyl]benzamide;
N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]-3-chlorothiophene-2-carboxamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]-4-chlorobenzamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]cyclohexanecarboxamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-{[2-(3,4-dichlorophenyl)-acetyl]amino}-N-hydroxyhexanamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]-2,5-dimethyl-3-furamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]-3,5-dimethylisoxazole-4-carboxamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-6-[(3-phenyl-propanoyl)amino]hexanamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]isonicotinamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]-2-methoxybenzamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]-4-methoxybenzamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-6-{[2-(4-nitrophenyl)acetyl]amino}hexanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-6-[(2-phenylacetyl)amino]hexanamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]quinoline-3-carboxamide;

N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]thiophene-3-carboxamide;

(E)-N-[(5R)-5-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-6-(hydroxyamino)-6-oxohexyl]-3-phenylprop-2-enamide;

(Z)-N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]octadec-9-enamide;

N-[(4R)-4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentyl]thiophene-2-carboxamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-{[(ethylamino)carbonyl]-amino}-N-hydroxypentanamide;

(2R)-5-[(Anilinocarbonyl)amino]-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypentanamide;

Octyl (4R)-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentylcarbamate;

4-Methoxyphenyl (4R)-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-5-(hydroxyamino)-5-oxopentylcarbamate;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-5-{[(diethylamino)-carbonyl]amino}-N-hydroxypentanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-{[(methylanilino)carbonyl]amino}pentanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-{[(1-methyl-1H-imidazol-4-yl)sulfonyl]amino}pentanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-[(2-morpholin-4-ylacetyl)amino]pentanamide;

(2R)-2-({[4-(But-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxy-5-{[2-(4-methylpiperazin-1-yl)acetyl]amino}pentanamide; and

(2R)-5-{[2-(Benzylamino)acetyl]amino}-2-({[4-(but-2-ynyloxy)phenyl]sulfonyl}amino)-N-hydroxypentanamide.

Other preferred TACE inhibitor compounds of the present invention include acetylenic β-sulfonamido and phosphinic acid amide hydroxamic acids such as

(1R,2R)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}(methyl)amino]-N-hydroxycyclohexanecarboxamide;

(1R, 2R)-2-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide;

3-({[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxypropanamide;

3-({[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxypropanamide;

(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclopentanecarboxamide;

(1R, 2S)-2-[{[4-(2-Butynyloxy)phenyl]sulfonyl} (methyl) amino] N-hydroxycyclopentanecarboxamide;

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxycyclohexanecarboxamide;

(Cis)-2-[{[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino]-N-hydroxycyclohexanecarboxamide;

(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N-hydroxybicyclo [2.2.1] heptane-2-carboxamide; and

(1R, 2R, 3S, 4R)-(Cis)-3-({[4-(2-butynyloxy)phenyl]sulfonyl} (methyl) amino)-N-hydroxybicyclo [2.2.1] heptane-2-carboxamide.

Another group of preferred TACE inhibitor compounds include acetylenic aryl sulfonamide and phosphinic acid amide hydroxamic acids such as

5-Bromo-2-{[4-(4-cyclobutylamino-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino}-N-hydroxy-3-methyl-benzamide;

5-Bromo-N-hydroxy-3-methyl-2-{methyl-[4-(4-methylamino-but-2-ynyloxy)-benzenesulfonyl]-amino}-benzamide;

5-Bromo-2-({4-[4-(3-dimethylamino-propylamino)-but-2-ynyloxy]-benzenesulfonyl}-methyl-amino)-N-hydroxy-3-methyl-benzamide;

5-Bromo-2-({4-[4-(2-dimethylamino-ethylamino)-but-2-ynyloxy]-benzenesulfonyl}-methyl-amino)-N-hydroxy-3-methyl-benzamide;

4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide;

5-Bromo-N-hydroxy-3-methyl-2-[methyl-(4-prop-2-ynyloxy-benzenesulfonyl)-amino]-benzamide;

5-Bromo-N-hydroxy-3-methyl-2-[methyl-(4-pent-2-ynyloxy-benzenesulfonyl)-amino]-benzamide;

5-Bromo-2-[(4-hept-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-benzamide;

5-Bromo-2-[(4-hex-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-benzamide;

5-Bromo-N-hydroxy-2-{[4-(4-methoxy-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino}-3-methyl-benzamide;

5-Bromo-N-hydroxy-3-methyl-2-{methyl-[4-(3-phenyl-prop-2-ynyloxy)-benzenesulfonyl]-amino}-benzamide;

5-Bromo-N-hydroxy-2-({4-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl}-methyl-amino)-3-methyl-benzamide;

5-Bromo-N-hydroxy-2-({4-[3-(2-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl}-methyl-amino)-3-methyl-benzamide;

5-Bromo-N-hydroxy-2-({4-[3-(4-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl}-methyl-amino)-3-methyl-benzamide;

2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-5-iodo-3-methyl-benzamide;

2-[Benzyl-(4-but-2-ynyloxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide;

5-Bromo-N-hydroxy-3-methyl-2-{methyl-[4-(4-pyrrolidin-1-yl-but-2-ynyloxy)-benzenesulfonyl]-amino}-benzamide;

5-Bromo-2-{[4-(4-diethylamino-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino}-N-hydroxy-3-methyl-benzamide;

5-Bromo-2-[(4-but-2-ynyloxy-benzenesulfonyl)-(4-methyl-piperazin-1-ylmethyl)-amino]-N-hydroxy-3-methyl-benzamide;

5-Bromo-N-hydroxy-3-methyl-2-(methyl-{4-[4-(tetrahydro-pyran-2-yloxy)-but-2-ynyloxy]-benzenesulfonyl}-amino)-benzamide;

5-Bromo-N-hydroxy-2-{[4-(4-hydroxy-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino}-3-methyl-benzamide; and

4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-(4-methyl-piperazin-1-ylmethyl)-biphenyl-3-carboxylic acid hydroxyamide dihydrochloride salt.

Still another preferred group of TACE inhibitor compounds of the present invention includes acetylenic aryl sulfonamide thiols such as

4-But-2-ynyloxy-N-((1R)-2-mercapto-1-methyl-ethyl)-N-methylbenzene-sulfonamide;

(2R)-2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}[2-(4-morpholinyl)ethyl]amino}-3-sulfanylpropanamide; and

4-(2-Butynyloxy)-N-[(1R)-1-methyl-2-sulfanylethyl]-N-[2-(4-morpholinyl)ethyl]benzenesulfonamide.

Yet another group of preferred TACE inhibitor compounds of the present invention includes acetylenic aryl and heteroaryl sulfonamide and phosphinic acid amide hydroxamic acids such as (3-[methyl-(4-but-2-ynyloxy-benzenesulfonyl-amino]-N-

hydroxy-2,6-dimethoxy-isonicotinamide and 3-(4-But-2-ynyloxy-benzenesulfonylamino)-N-hydroxy-2,6-dimethoxy-isonicotinamide.

Other preferred TACE inhibitor compounds of the present invention include alkynyl containing hydroxamic acid compounds such as

2-(4-But-2-ynyloxy-benzenesulfonyl)-N-hydroxy-2-methyl-3-pyridin-3-yl-propionamide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-N-hydroxy-propionamide;

2-(4-But-2-ynyloxy-benzesulfonyl)-N-hydroxy-2-methyl-3-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-propionamide;

3-Biphenyl-4-yl-2-(4-but-2-ynyloxy-benzenesulfonyl)-N-hydroxy-2-methyl-propionamide;

2-(4-But-2-ynyloxy-phenysulfanyl)-octanoic acid hydroxamide;

2-(But-2-ynyloxy-benzenesulfonyl)-octanoic acid hydroxamide;

2[(R)-(4-Butyl-2-ynyloxy)-sulfinyl-N-hydroxyoctanamide;

2[(S)-(4-Butyl-2-ynyloxy)-sulfinyl-N-hydroxyoctanamide;

3-(4-But-2-ynyloxy-phenoxy)-N-hydroxy-propionamide

4-(4-But-2-ynyloxy-phenoxy)-N-hydroxy-butyramide;

2-(4-But-2-ynyloxy-phenoxy)-N-hydroxy-acetamide;

4-(4-But-2-ynyloxy-phenyl)-N-hydroxy-butyramide;

Quinoline-2-carboxylic acid [5-(4-but-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino]-hexanoic acid hydroxyamide;

N-[5-(4-But-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl]-2-phenethyl-benzamide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-6-[2-(3,4-dichloro-phenyl)-acetylamino]-hexanoic acid hydroxyamide;

Quinoline-3-carboxylic acid [5-(4-but-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-6-(4-thiophen-2-yl-butyrylamino)-hexanoic acid hydroxyamide;

9H-Xanthene-9-carboxylic acid [5-(4-but-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-6-diphenylacetylamino-hexanoic acid hydroxyamide;
Isoquinoline-1-carboxylic acid [5-(4-but-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl]-amide;
6-(2-Benzo[b]thiophen-3-yl-acetylamino)-2-(4-but-2-ynyloxy-phenyl-sulfanyl)-hexanoic acid hydroxyamide;
Quinoline-2-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentyl]-amide;
2-(4-But-2-ynyloxy-benzenesulfinyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino]-hexanoic acid hydroxyamide;
N-[5-(4-But-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentyl]-2-phenethyl-benzamide;
2-(4-But-2-ynyloxy-benzenesulfinyl)-6-[2-(3,4-dichloro-phenyl)-acetylamino]-hexanoic acid hydroxyamide;
Quinoline-3-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentyl]-amide;
2-(4-But-2-ynyloxy-benzenesulfinyl)-6-(4-thiophen-2-yl-butyrylamino)-hexanoic acid hydroxyamide;
9H-Xanthene-9-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentyl]-amide;
2-(4-But-2-ynyloxy-benzenesulfinyl)-6-diphenylacetylamino-hexanoic acid hydroxyamide;
Isoquinoline-1-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentyl]-amide;
6-(2-Benzo[b]thiophen-3-yl-acetylamino)-2-(4-but-2-ynyloxy-benzene-sulfinyl)-hexanoic acid hydroxyamide;
2-(4-But-2-ynyloxy-benzenesulfinyl)-6-(2-1H-indol-3-yl-acetylamino)-hexanoic acid hydroxyamide;
Quinoline-2-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentyl]-amide;
2-(4-But-2-ynyloxy-benzenesulfonyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino]-hexanoic acid hydroxyamide;

N-[5-(4-But-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentyl]-2-phenethyl-benzamide;

2-(4-But-2-ynyloxy-benzenesulfonyl)-6-[2-(3,4-dichloro-phenyl)-acetyl-amino]-hexanoic acid hydroxyamide;

Quinoline-3-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfonyl)-5-5-hydroxycarbamoyl-pentyl]-amide;

9H-Xanthene-9-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-ynyloxy-benzenesulfonyl)-6-diphenylacetylaminohexanoic acid hydroxyamide;

Isoquinoline-1-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentyl]-amide;

6-(2-Benzo[b]thiophen-3-yl-acetylamino)-2-(4-but-2-ynyloxy-benzene-sulfonyl)-hexanoic acid hydroxyamide;

Quinoline-2-carboxylic acid {[5-(4-but-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino]-acetylamino}hexanoic acid hydroxyamide;

N-{[5-(4-But-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl-carbamoyl]-methyl}-2-phenethyl-benzamide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-6-{2-[2-(3,4-dichloro-phenyl)-acetylamino]-acetylamino}-hexanoic acid hydroxyamide;

Quinoline-3-carboxylic acid {[5-(4-but-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

9H-Xanthene-9-carboxylic acid {[5-(4-but-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-6-(2-diphenylacetylamino-acetylamino)-hexanoic acid hydroxyamide;

Isoquinoline-1-carboxylic acid {[5-(4-but-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

1-Methyl-1H-pyrrole-2-carboxylic acid {[5-(4-but-2-ynyloxy-phenyl-sulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

6-[2-(2-Benzo[b]thiophen-3-yl-acetylamino)-acetylamino]-2-(4-but-2-ynyloxy-phenylsulfanyl hexanoic acid hydroxyamide;

Quinoline-2-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

2-(4-But-2-ynyloxy-benzenesulfinyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino]-acetylamino}-hexanoic acid hydroxyamide;

N-{[5-(4-But-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentyl-carbamoyl]-methyl}-2-phenethyl-benzamide;

2-(4-But-2-ynyloxy-benzenesulfinyl)-6-{2-[2-(3,4-dichloro-phenyl)-acetylamino]-acetylamino}-hexanoic acid hydroxyamide;

Quinoline-3-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}amide;

2-(4-But-2-ynyloxy-benzenesulfinyl)-6-[2-(4-thiophen-2-yl-butyrylamino)-acetylamino]-hexanoic acid hydroxyamide;

9H-Xanthene-9-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

2-(4-But-2-ynyloxy-benzenesulfinyl)-6-(2-diphenylacetylamino-acetylamino)-hexanoic acid hydroxyamide;

1-Methyl-1H-pyrrole-2-carboxylic acid {[5-(4-but-2-ynyloxy-benzene-sulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide ;

2-(4-But-2-ynyloxy-benzenesulfonyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino]-acetylamino}-hexanoic acid hydroxyamide;

N-{[5-(4-But-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-2-phenethyl-benzamide;

2-(4-But-2-ynyloxy-benzenesulfonyl)-6-{2-[2-(3,4-dichloro-phenyl)-acetylamino]-acetylamino}-hexanoic acid hydroxyamide;

Quinoline-3-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}amide;

9H-Xanthene-9-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

2-(4-But-2-ynyloxy-benzenesulfonyl)-6-(2-diphenylacetylamino-acetylamino)-hexanoic acid hydroxyamide;

Isoquinoline-1-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfonyl)-

5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

6-[2-(2-Benzo[b]thiophen-3-yl-acetylamino)-acetylamino]-2-(4-but-2-ynyloxy benzenesulfonyl hexanoic acid hydroxyamide;

2-(4-But-2-ynyloxy-benzenesulfonyl)-6-[2-(2-1H-indol-3-yl-acetylamino)-acetylamino]-hexanoic acid hydroxyamide;

2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-{4-[2-(1-piperidinyl)ethoxy phenyl}butanamide;

2-{[4-(2-butynyloxy)phenyl]sulfonyl}-7-cyano-N-hydroxy heptanamide;

2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-cyclohexyl-N-hydroxyacetamide;

2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-cyclohexyl-N-hydroxyacetamide;

2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-cyclohexyl-N-hydroxyacetamide;

2-{[4-(2-butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-(4-methoxyphenyl) acetamide;

(2R)-2-{[4-(2-butynyloxy)phenyl] sulfinyl}-N-hydroxy-2-(4-methoxyphenyl) ethanamide;

(2S)-2-{[4-(2-butynyloxy)phenyl] sulfinyl}-N-hydroxy-2-(4-methoxyphenyl) ethanamide;

2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(4-methoxyphenyl) acetamide;

2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-(4-chlorophenyl)-N-hydroxyacetamide;

2-{[4-(2-butynyloxy)phenyl] sulfinyl}-2-(4-chlorophenyl) N-hydroxyacetamide;

2-{[4-(2-butynyloxy)phenyl]sulfonyl-2-(4-chlorophenyl)-N-hydroxy-acetamide;

2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-(3-chlorophenyl)-N-hydroxyacetamide;

2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(3-chlorophenyl)-N-hydroxyacetamide;

2-(4-bromophenyl)-2-{[4-(2-butynyloxy)phenyl]sulfanyl-N-hydroxyacetamide;

(2S)-2-(4-bromophenyl)-2-{[4-(2-butynyloxy)phenyl]sulfinyl-N-hydroxy-acetamide;

(2R)-2-(4-bromophenyl)-2-{[4-(2-butynyloxy)phenyl] sulfinyl-N-hydroxy-acetamide;

2-(4-bromophenyl)-2-{[4-(2-butynyloxy)phenyl]sulfonyl-N-hydroxy-acetamide;

2{[4-(2-butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-[4-(2-thienyl)phenyl]-acetamide;

(2R)-2-{[4-(2-butynyloxy)phenyl] sulfinyl}- N-hydroxy-2-[4-(2-thienyl)-phenyl]ethanamide;

2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-[4-(2-thienyl)-phenyl]acetamide;

2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-(1-napthyl)acetamide;

2-{[4-(2-Butynyloxy)phenyl]sulfinyl}-N-hydroxy-2-(1-napthyl)acetamide;

2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(1-napthyl)acetamide;
2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-(4-fluorophenyl)-N-hydroxy-2-(1-napthyl)acetamide;
2-{[4-(2-butynyloxy)phenyl]sulfinyl-2-(4-fluorophenyl)-N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl-2-(4-fluorophenyl)-N-hydroxyacetamide;
2-(2-methoxyphenyl)-2-{[4-(2-butynyloxy)phenyl]sulfanyl-N-hydroxy-acetamide;
2-(2-methoxyphenyl)-2-{[4-(2-butynyloxy)phenyl]sulfinyl}-N-hydroxy-acetamide;
2-{[4-(2-butynyloxy)phenyl]sulfanyl-N-hydroxy-2-(4-ethoxyphenyl) acetamide;
2-{[4-(2-Butynyloxy)phenyl] sulfinyl-N-hydroxy-2-(4-ethoxyphenyl) acetamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl-2-(4-chlorophenyl)-N-hydroxyacetamide;
2-{[4-(2-Butynyloxy)phenyl]sulfanyl-N-hydroxy-2-(3-bromophenyl) acetamide;
(2R)-2-{[4-(2-butynyloxy)phenyl]sulfinyl-N-hydroxy-2-(3-bromophenyl) acetamide;
(2S)-2-{[4-(2-butynyloxy)phenyl] sulfinyl-N-hydroxy-2-(3-bromophenyl) acetamide;
2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-2-(3-bromophenyl)-N-hydroxyacetamide;
2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-isopropyl-N-hydroxyacetamide;
R-2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-isopropyl-N-hydroxyacetamide;
S-2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-isopropyl-N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-isoprpyl-N-hydroxyacetamide;
2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-phenyl-N-hydroxyacetamide;
R-2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-phenyl-N-hydroxyacetamide;
S-2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-phenyl-N-hydroxyacetamide;
2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-(2-naphthyl)-N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-(2-naphthyl)-N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(2-naphthyl)-N-hydroxyacetamide;
Tert-butyl-4-[1-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(hydroxyamino)-2-oxoethyl]-1-piperidine carboxylate;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(4-piperidinyl) acetamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-[1-(4-methoxybenzyl)-4-piperidinyl] acetamide;
2-(1-benzoyl-4-piperidinyl)-2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-acetamide;
2-(1-acetyl-4-piperidinyl)-2-{[4-(2-butynyloxy)phenyl]sulfonyl-N-hydroxy-acetamide;

2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-tetrahydro-2H-pyran-4yl-acetamide;

2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-tetrahydro-2H-thiopyran-4yl-acetamide;

2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(1-oxidotetrahydro-2H-thiopyran-4yl) acetamide; and

2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(1,1-dioxidotetrahydro-2H-thiopyran-4yl) acetamide.

Other preferred TACE inhibitor compounds of the present invention include carboxamides and hydroxamides such as

1-(4-Bromo-benzyl)-4-(4-but-2-ynyxoy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-methoxy-benzyl)-piperdine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-chloro-benzyl)-piperdine-4-carboxylic acid hydroxyamide;

1-Benzyl-4-(4-but-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxamide;

1-(4-Bromo-benzyl)-4-(4-pent-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxyamide;

1-(4-Bromo-benzyl)-4-(4-oct-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-fluoro-benzyl)-piperdine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-cyano-benzyl)-piperidine-4- carboxylic acid hydroxamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-methyl-benzyl)-piperidine-4- carboxylic acid hydroxamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(3,4- dichloro-benzyl)-piperidine-4-carboxylic acid hydroxamide;

1-(4-Bromo-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxyamide;

1-(4-Bromo-benzyl)-4-[4-(4-piperdin-4-yl-but-2-ynyloxy)-benzenesulfonyl]-piperdine-4-carboxylic acid hydroxyamide;

1-(4-Bromo-benzyl)-4-[4-(4-morpholin-4-yl-but-2-ynyloxy)-benzene-sulfonyl]-piperdine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-phenylsulfanyl)-4-hydroxycarbamoyl-piperidine-1-carboxylic acid tert-butyl ester;

4-(4-But-2-ynyloxy-phenylsulfanyl)-piperidine-4-carboxylic acid hydroxyamide

1-(4-Bromo-benzyl)-4-(4-but-2-ynyloxy-phenylsulfanyl)-piperidine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-phenylsulfanylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfinylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxytetrahydro-2H-pyran-4-carboxamide;

1-benzyl-4-{[3-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-piperdine carboxamide;

4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-isopropyl-4-piperidine carboxamide;

4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-(3-pyridinylmethyl)-4-piperidine carboxamide;

3-{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-ethyl-N-hydroxy-3-piperidine-carboxamide;

3-{[4-(2-butynyloxy)phenyl]sulfonyl}-1-(4-chlorobenzyl)-N-hydroxy-3-piperidinecarboxamide;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-piperidine-4-carboxylic acid hydroxyamide;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-(3-pentanyl)-piperidine-4-carboxylic acid hydroxyamide;

1-(4-Methoxy-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide;

1-(4-Chloro-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide;

tert-butyl-4-({[4-(2-butynyloxy)phenyl]sulfanyl}methyl)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxylate;

4-({[4-(But-2-ynyloxy)phenyl]thio}methyl)-N-hydroxypiperidine-4- carboxamide;

tert-Butyl-4-({[4-(2-butynyloxy)phenyl]sulfinyl}methyl)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxylate;

4-[[[4-(2-Butynyloxy)phenyl]sulfinyl]methyl]-N-hydroxy-4-piperidine-carboxamide;

tert-Butyl-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]piperidine-1-carboxylate;

tert-butyl-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxyla;

1-Acetyl-4-[[[4-(2-butynyloxy)phenyl]sulfonyl]methyl]-N-hydroxy-4-piperidinecarboxamide;

1-(2-Butynyl)-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-piperidinecarboxamide hydrochloride;

N-1-(tert-Butyl)-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-4-hydroxy-1,4-[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-4-hydroxy-1,4-l]sulfonyl}-methyl)-N~4~-hydroxy-1,4-piperidinedicarboxamide;

Methyl 4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxylate;

Benzyl 4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxylate;

1-Benzyl-4-({[4-(2-butynyloxy)phenyl] sulfonyl} methyl)-N-hydroxy-4-butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-piperidinecarboxamide;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-[(2,2,5-trimethyl-1,3-dioxan-5-yl)carbonyl]-4-piperidinecarboxamide;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoyl]-4-piperidinecarboxamide;

1-[Amino(imino)methyl]-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-l]-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-oxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-piperidinecarboxamide;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(4-hydroxy-2-butynyl)-henyl]sulfonyl}methyl)-N-hydroxy-1-(4-hydroxy-2-butynyl)-4-piperidinecarboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-1-ethyl-N-hydroxypiperidine-4-carboxamide triflouroacetic acid salt;

2-chloro-5-(chloromethyl) thiophene4-({[4-(But-2-ynyloxy)phenyl]-sulfonyl}-methyl)-1-[(5-chlorothien-2-yl)methyl]-N- hydroxypiperidine-4-carboxamide triflouroacetic acid salt;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(pyridin-4-ylmethyl)piperidine-4-carboxamide triflouroacetic acid salt;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(pyridin-3 ylcarbonyl)piperidine-4-carboxamide triflouroacetic acid salt;

1-Benzoyl-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(thien-2- ylcarbonyl) piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-1-ethyl-N-4-hydroxy-piperidine-1,4-dicarboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-4-hydroxy-N-1- phenyl-piperidine-1,4-dicarboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-1-,N-1-diethyl-N-4-hydroxypiperidine-1,4-dicarboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(morpholin-4-ylcarbonyl)piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-4-hydroxy-N-1-methyl-N-1-phenylpiperidine-1,4-dicarboxamide;

Octyl-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl] piperidine-1-carboxylate;

4-Methoxyphenyl4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxy-amino) carbonyl]piperidine-1-carboxylate;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(phenylsulfonyl) piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-[(1-methyl-1H-imidazol-4-yl)sulfonyl]piperidine-4-carboxamide;

1-[2-(Benzylamino)acetyl]-4-({[4-(but-2-ynyloxy)phenyl]-sulfonyl}methyl)-N-hydroxypiperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(2-morpholin-4-ylacetyl)piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-[2-(4-methyl-piperazin-1-yl)acetyl]piperidine-4-carboxamide;

1-Acetyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

1-Benzoyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

1-(4-Methoxybenzoyl)-4-(4-but-2-ynyloxy benzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(pyrrolidine-1-carbonyl)-4-piperidinecarboxamide;

Ethyl 4-(4-but-2-ynyloxybenzenesulfonyl)-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxylate;

4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(trifluoromethyl)sulfonyl]-4-piperidinecarboxamide;

4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(3-pyridinylcarbonyl)- 4-piperidinecarboxamide;

4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(2-thienylcarbonyl)- 4-piperidinecarboxamide;

4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(4-methoxyphenyl)-sulfonyl]-4-piperidinecarboxamide;

4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(2,2,5-trimethyl-1,3-dioxan-5-yl)carbonyl]-4-piperidinecarboxamide;

Tert-butyl-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxalate;

4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-piperidinecarboxamide hydrochloride;

Methyl ({4-{[4-(2-butynyloxy)phenyl]sulfonyl}-4-[(hydroxyamino)carbonyl]-1-piperidinyl}methyl)benzoate hydrochloride;

4-({4-{[4-(2-butynyloxy)phenyl]sulfonyl}-4-[(hydroxyamino)carbonyl]-1-piperidinyl}methyl)benzoic acid hydrochloride;

1-[4-(Aminocarbonyl)benzyl]-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-piperidinecarboxamide hydrochloride;

Tert-butyl 4-{[4-(but-2-ynyloxy)phenyl]sulfinyl}-4-[(hydroxyamino)-carbonyl]piperidine-1-carboxalate;

4-(4-(But-2-ynyloxy-benzenesulfinyl)-piperidine-4-carboxylic acid hydroxamide hydrochloride; and

1-(4-Bromo-benzyl)-4-(4-But-2-ynyloxy-benzenesulfinyl)-piperidine-4-carboxylic acid hydroxamide hydrochloride;

In the present invention "an effective amount" of the EGF receptor kinase inhibitor compound will vary with inter alia the individual patient and the severity of the disease, however generally it will be at least about 5 mg/kg. A preferred range is about 10 to 50 mg/kg.

In the present invention "an effective amount" of the TACE inhibitor compound will vary with a variety of factors including the individual patient and the severity of the disease. Typically the effective amount will be at least about 5 mg/kg. A preferred range is about 20 to 40 mg/kg.

The dosing schedule of the drug(s) may be from once to several times per day or may be less frequent. Preferably the dosing will be less frequent, for example dosing every other day, every third day or once a week.

In the present invention, the terms TACE inhibitor, TACE inhibitor compound, EGF receptor kinase inhibitor, and EGF receptor kinase inhibitor compound include all optical isomers and diastereomers as well as pharmaceutically acceptable salts.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic

bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, when a compound of this invention contains an acidic moiety.

The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. It is recognized that one optical isomer, including diastereomer and enantiomer, or stereoisomer may have favorable properties over the other. Thus when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

An effective amount of the compound[s] of the invention are provided to the patient. The compounds may be provided orally, in liquid or solid form, or by injection. In addition the compound may be provided to the patient via a pro-drug route wherein the patient actually converts in vivo a substance given to him or her to one or more of the TACE inhibitors or EGF receptor kinase inhibitors of the present invention.

The following examples are merely illustrative of the present invention. The invention is not to be limited thereby.

Example 1

The *bpk* model of ARPKD

This model arose from a spontaneous mutation in a colony of BALB/C mice. Affected animals have many similarities to the human disease including collecting tubule (CT) cysts and biliary ectasia and fibrosis. The kidney disease has a consistent and severe phenotype. Mice homozygous for the *bpk* mutation have microscopic evidence of cyst formation at birth. Proximal tubule (PT) cysts are present at birth, which are gradually replaced by CT cysts as the disease progresses. Cyst expansion and kidney fibrosis result in death due to renal failure at 24-28 days. Heterozygotes show no phenotypic abnormalities and are identified by their ability to breed affected offspring. Unaffected (noncystic) littermates of cystic *bpk* mice are either wild-type or heterozygous at the *bpk* locus.

TGF-α expression in *bpk* mice

Kidneys were obtained from cystic *bpk* mice and noncystic littermates at postnatal days 7, 14 and 21. Immunohistology was performed formaldehyde-fixed specimens embedded in plastic [See Sweeney WE et al.: Treatment of polycystic kidney disease with a novel tyrosine kinase inhibitor, *Kidney Int.* 57:33-40, 2000.] Primary antibody was a polyclonal anti-TGF-α (Chemicon, Temecula, CA) directed against recombinant 6 kD human TGF-α and reactive to mouse. Tubular localization of antibody staining was assessed by staining of serial sections with segment-specific biotinylated lectins.

Protein was isolated from whole kidneys by homogenization in RIPA buffer (phosphate buffered saline containing 1% nonidet P-40, 0.5% sodium deoxycholate, 0.1% SDS) with inhibitors (0.1mg/ml aprotinin, 5μg/ml leupeptin, 50μg/ml pepstatin, 1mM EDTA, 1mM PMSF and 1:100 v/v phosphatase inhibitor cocktail). Protein content of all samples was determined using the BCA protein assay kit (Pierce, Rockford, IL) and equal loading confirmed by Ponseau S solution staining of membranes following transfer.

For Western blotting, 30μg of total protein lysate was diluted in SDS reducing buffer (62.5mM Tris-HCL, pH 6.8, 25% v/v glycerol, 2% w/v SDS, 0.01% w/v bromophenol blue, 5% v/v β-mercaptoethanol) and subjected to SDS-PAGE electrophoresis using a 12% separating gel. Samples were transferred to a nitrocellulose membrane, hybridized with blocking buffer (5% dry milk, 0.05% Tween 20), then hybridized with mouse monoclonal anti-TGF-α (Research Diagnostics, Flanders, NJ). Membranes were washed and hybridized with peroxidase conjugated anti-mouse antibody. Membranes were treated with ECL chemiluminesence reagent (Amersham Pharmacia Biotech, Piscataway, NJ) and exposed to autoradiography film.

Cyst fluid from day 21 *bpk* mice was also examined for the presence of TGF-α by immunoprecipitation. 200 μg of total cyst fluid protein was immunoprecipitated with 2μg of primary antibody (polyclonal anti-TGF-α, Santa Cruz, CA), then Protein A/G PLUS-agarose (Santa Cruz) added and the incubation continued. Pellets were collected by centrifugation, washed and resuspended in 1X SDS reducing buffer and boiled for 2-3 minutes.

Example 2

Comparison Of 1-Acetyl-4-(4-But-2-ynyloxy-Benzenesulfonyl)-2,3,4,5-Tetrahydro-1H-[1,4]Benzodiazepine-3-Carboxylic Acid Hydroxyamide Treatment Of *bpk* Mice And 1-Benzyl-4-[4-(4-Chloro-Phenoxy)-Benzenesulfonyl]-Piperidine-4-Carboxylic Acid Hydroxamide, (An MMP Inhibitor Without TACE Activity) Treatment Of *bpk* Mice

1-Acetyl-4-(4-But-2-ynyloxy-Benzenesulfonyl)-2,3,4,5-Tetrahydro-1H-[1,4]Benzodiazepine-3-Carboxylic Acid Hydroxyamide Treatment

Cystic *bpk* mice and phenotypically normal littermates were injected with a dose of 100 mg/kg/dose of 1-acetyl-4-(4-but-2-ynyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1h-[1,4]benzodiazepine-3-carboxylic acid hydroxyamide given intraperitoneally once daily, in a vehicle containing 0.5% methocellulose (Fluka Biochemica, Ronkonkoma, NY) and 2% Tween 80 (JT Baker, Phillipsburg, NJ), beginning at postnatal day 7. Age-matched untreated cystic *bpk* mice and their noncystic littermates served as controls. At day 21, mice were sacrificed. Blood was obtained by orbital puncture prior to sacrifice. Kidney weight and body weight for treated and untreated cystic and noncystic mice were measured at sacrifice. Blood urea nitrogen (BUN) was assessed using a colorimetric assay. Serum creatinine was assessed using standard techniques in the hospital laboratory. Differences in clinical and laboratory parameters between treated and untreated cystic and noncystic mice were analyzed by two-tailed Student's t-test.

Kidneys were fixed in 4% paraformaldehyde and embedded in plastic. Segment-specific localization of cysts was assessed using lectins specific to proximal tubule (*Lotus tetragonolobus*, LTA), and collecting tubule (*Dolichos biflorus* agglutinin, DBA). Serial LTA and DBA stained sections were examined by light microscopy and assessed for severity of cystic dilatations in PTs and CTs, expressed on a scale of 0 to 5 using a modified cystic index:

0 = No cysts
1 = $\leq$ 0.11 mm
2 = 0.12-0.19 mm
3 = 0.20-0.27 mm
4 = 0.28-0.35 mm
5 = $\geq$ 0.36 mm

The total number of CT (DBA+/LTA-) cysts and PT (LTA+/DBA-) cysts within a section were counted and expressed as a ratio.

In order to determine if inhibition of secreted TGF-α affected total kidney expression of TGF-α protein, TGF-α expression in 1-acetyl-4-(4-but-2-ynyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1h-[1,4]benzodiazepine-3-carboxylic acid hydroxyamide-treated and untreated cystic and noncystic animals was assessed by Western analysis as described in Example 1.

Treatment With 1-Benzyl-4-[4-(4-Chloro-Phenoxy)-Benzenesulfonyl]-Piperidine-4-Carboxylic Acid Hydroxamide, An MMP Inhibitor Without TACE Activity

Two litters of *bpk* mice and their noncystic littermates were treated with dosages of 50 mg/kg/day of 1-benzyl-4-[4-(4-chloro-phenoxy)-benzenesulfonyl]-piperidine-4-carboxylic acid hydroxamide given as once daily IP injections. Mice were treated from day 7 of life until day 21, then sacrificed. Analysis of 1-benzyl-4-[4-(4-chloro-phenoxy)-benzenesulfonyl]-piperidine-4-carboxylic acid hydroxamide treated mice included assessment of kidney weight to body weight ratio. The results are listed below in Tables 1, 2, and 3.

Table 1. Clinical Parameters of 1-Acetyl-4-(4-But-2-ynyloxy-Benzenesulfonyl)-2,3,4,5-Tetrahydro-1H-[1,4]Benzodiazepine-3-Carboxylic Acid Hydroxyamide Treated and Untreated Mice

Treatment Group	**Kidney Weight (grams)**	**Body Weight (grams)**	**Kidney Weight to Body Weight (percent)**	**BUN (mg/dl)**	**Creatinine (mg/dl)**
P-21 Cystic (n=15)	1.83 +/- 0.6	9.3 +/- 2.2	19.7 +/- 3.4	50 +/- 9[a]	0.28 +/- 0.13[a]
P-21 Cystic+A (n=6)	0.93 +/- 0.2 **	8.2 +/- 1.3	11.2 +/- 1.3**	33 +/- 4[b] **	0.18 +/- 0.05[b]
P-21 Noncystic (n=30)	0.13 +/- 0.01	9.1 +/- 1.0	1.5 +/- 0.1	19 +/- 4[c]	0.14 +/- 0.07[e]
P-21 Noncystic + A (n=27)	0.13 +/- 0.01	8.5 +/- 1.0	1.5 +/- 0.1	17 +/- 4[d]	0.15 +/- 0.05[e]

[a] n=5; [b] n=4; [c] n=12; [d] n=14; [e] n=10

A=1-Acetyl-4-(4-But-2-ynyloxy-Benzenesulfonyl)-2,3,4,5-Tetrahydro-1H-[1,4]Benzodiazepine-3-Carboxylic Acid Hydroxyamide

** $p<0.01$ cystic treated compared to cystic untreated

Table 2. Kidney Histology of 1-Acetyl-4-(4-But-2-ynyloxy-Benzenesulfonyl)-2,3,4,5-Tetrahydro-1H-[1,4]Benzodiazepine-3-Carboxylic Acid Hydroxyamide Treated and Untreated Cystic Mice

Treatment Group	CT Cystic Index (graded 1-5)	CT Cyst Size Range (mm)	PT Cystic Index (graded 1-5)	PT Cyst Size Range (mm)	Cystic CT/PT Ratio
Cystic No Treatment	4.8 +/- 0.4	0.012-0.41	1.4 +/- 0.5	0.012-0.13	8
Cystic +A	3.2 +/- 0.4 **	0.012-0.29	1.8 +/- 0.4	0.012-0.17	1.2**

A = 1-acetyl-4-(4-but-2-ynyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid hydroxyamide
** $p<0.01$ cystic treated compared to cystic untreated

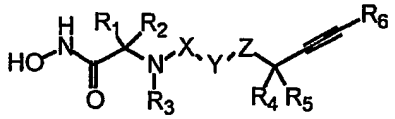
Table 3. MMP activity (IC 50) and treatment effect of A versus B

Treatment	MMP-1	MMP-9	MMP-13	TACE	Cystic Kidney Weight to Body Weight (percent)
A	6.6	12	3	8.4	11.2 +/- 1.3
B	801	1.1	0.9	0	15.3 +/- 1.7
No Treatment	0	0	0	0	19.7 +/- 3.4

A = 1-acetyl-4-(4-but-2-ynyloxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1H-[1,4]benzodiazepine-3-carboxylic acid hydroxyamide
B = 1-Benzyl-4-[4-(4-chloro-phenoxy)-benzenesulfonyl]-piperidine-4-carboxylic acid hydroxamide

What is claimed is:

1. A method for treating, inhibiting the progression of, or eradicating polycystic kidney disease in a mammal in need thereof which comprises providing to said mammal an effective amount of a TACE inhibitor compound.
2. A method for treating, inhibiting the progression of, or eradicating polycystic kidney disease in a mammal in need thereof which comprises providing to said mammal a combination of an effective amount of a TACE inhibitor compound and an effective amount of an EGF receptor kinase inhibitor.
3. The method according to claim 1 or 2 wherein the TACE inhibitor compound is a compound of formula I:



I

wherein:

X is SO_2 or -P(O)-R_{10};

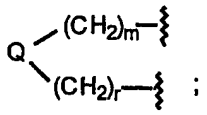
Y is aryl or heteroaryl, with the proviso that X and Z may not be bonded to adjacent atoms of Y;

Z is O, NH, CH_2 or S;

R_1 is hydrogen, aryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms;

R_2 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl of 3-6 carbon atoms, C_4-C_8 cycloheteroalkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms;

or R_1 and R_2, together with the atom to which they are attached, may form a ring wherein R_1 and R_2 represent a divalent moiety of the formula:



wherein

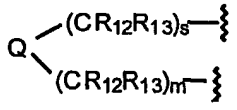
Q = a carbon-carbon single or double bond, O, S, SO, SO_2, -N-R_{11}, or -$CONR_{14}$;

m = 1-3;

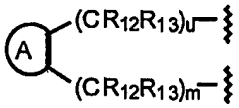
r = 1 or 2, with the proviso that when Q is a bond, r is equal to 2;

R_3 is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, C4-C8 cycloheteroalkyl, aralkyl, or heteroaralkyl;

or R_1 and R_3, together with the atoms to which they are attached, may form a 5 to 8 membered ring wherein R_1 and R_3 represent divalent moieties of the formulae:



; and



wherein Q and m are as defined above;

A is aryl or heteroaryl;

s is 0-3;

u is 1-4;

R_4 and R_5 are each, independently, hydrogen or alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_6 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C_5-C_8-cycloheteroalkyl;

R_8 and R_9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, aralkyl, heteroaryl, heteroaralkyl, or -C4-C_8-cycloheteroalkyl;

R_{10} is alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl or heteroaryl;

R_{11} is hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, -$S(O)_nR_8$, -$COOR_8$, -$CONR_8R_9$, -$SO_2NR_8R_9$ or -COR_8;

R_{12} and R_{13} are independently selected from H, -OR_8, -NR_8R_9, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, -$COOR_8$; -$CONR_8R_9$; or R_{12} and R_{13} together form a -C_3-C_6-cycloalkyl of 3-6 carbon atoms or a -

C_5-C_8-cycloheteroalkyl ring; or R_{12} and R_{13}, together with the carbon to which they are attached, form a carbonyl group;

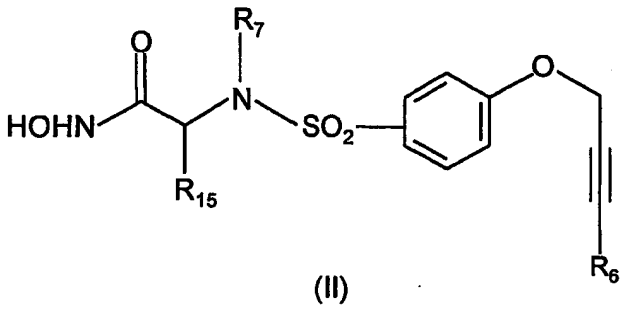
with the proviso that R_{10} and R_{12} or R_{11} and R_{12} may form a cycloheteroalkyl ring when they are attached to adjacent atoms;

R_{14} is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms or cycloalkyl of 3-6 carbon atoms;

and n is 0-2;

or a pharmaceutically acceptable salt thereof.

4. The method according to claim 3 wherein the compound is a compound of formula II:



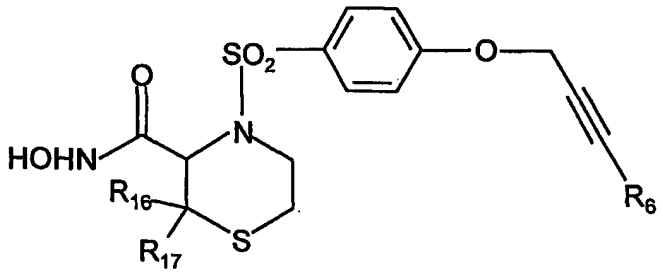
(II)

wherein

R_6 is as defined in claim 3; R_7 is H or alkyl; and R_{15} is alkyl.

5. The method according to claim 4 wherein R_6 is CH_3 or CH_2OH; R_7 is H or methyl; and R_{15} is isopropyl or $CH(CH_3)OH$.

6. The method according to claim 3 wherein the compound is a compound of formula III:



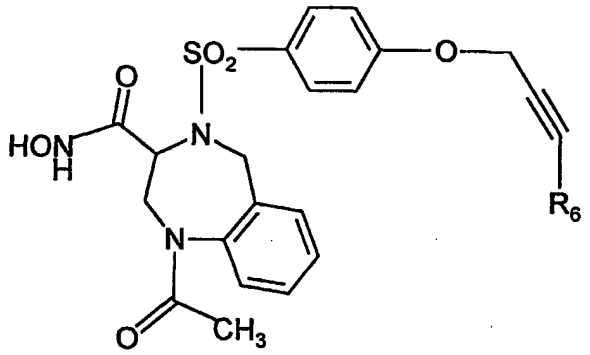
(III)

wherein R_6 is defined as in claim 3 with methyl and CH_2OH being preferred; and R_{16} and R_{17} are alkyl preferably methyl.

7. The method according to claim 6 wherein R_6 is methyl or CH_2OH; and R_{16} and R_{17} are methyl.

8. The method according to claim 3 wherein the compound is selected from the group consisting of 4-(4-but-2-ynyloxy-benzenesulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid hydroxyamide; (3S)-N-hydroxy-4-({4-[(4-hydroxy-2-butynyl)oxy]phenyl}sulfonyl)-2,2-dimethyl-3-thiomorpholinecarboxamide; (2R)-N-hydroxy-2-[({4-[(4-hydroxy-2-butynyl)oxy]phenyl}sulfonyl)(methyl)amino]-3-methylbutanamide; and (2R,3S)-2-({[4-(2-butynyloxy)phenyl]sulfonyl}amino)-N,3-dihydroxybutanamide; or a pharmaceutically acceptable salt thereof.

9. A method for treating, inhibiting the progression of, or eradicating polycystic kidney disease in a mammal in need thereof which comprises providing to said mammal an effective amount of a TACE inhibitor compound of formula IV:



(IV)

wherein R_6 is as defined in claim 3.

10. The method according to claim 9 wherein R_6 is methyl.

11. The method according to claim 2 wherein the EGF receptor kinase inhibitor is 4-dimethylamineo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide.

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(54) Title: NOVEL SULFONAMIDE DERIVATIVES, INTERMEDIATE THEREOF, ITS PREPARATION METHODS, AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

(57) Abstract: The present invention relates to a novel sulfonamide derivatives and novel intermediates thereof, preparation thereof, and a pharmaceutical composition comprising the same, and more particularly, to novel sulfonamide derivatives and intermediates thereof that are used as angiogenesis controlling material and that can inhibit overexpression of matrix metalloproteinase that decomposes protein constituents in extracellular matrix and basement membranes of connective tissues, and preparation methods thereof, and a pharmaceutical composition comprising the same.

NOVEL SULFONAMIDE DERIVATIVES, INTERMEDIATE THEREOF, ITS PREPARATION METHODS, AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

BACKGROUND OF THE INVENTION

(a) Field of the Invention

The present invention relates to novel sulfonamide derivatives having superior matrix metalloproteinase (MMP) inhibiting activity, and novel intermediates thereof, preparation methods thereof, and a pharmaceutical composition comprising the sulfonamide derivatives.

(b) Description of the Related Art

Angiogenesis, a process during which endothelial cells proliferate from existing capillaries to produce novel capillaries, occurs only under normal physiological functions such as during wound healing, ovulation of females, fetal development processes during pregnancy, etc., and it occurs little under normal conditions exclusive of the above conditions in adults. Angiogenesis is strictly controlled by a balance between angiogenic factors and angiogenesis inhibitors (Folkman, J. and Cotran, Int. Rev. Exp. Pathol. 1976, 16. 207-248. Folkman. J. Nat. Med. 1995. 1, 27-31.).

Erroneous control of angiogenesis is known to cause various diseases (Drug Design and Discovery, 1991, 8, 3. Opthalmol. 1995, 102. 1261-1262. Cell, 1996, 86, 353-364, Biochem. Pharmacol. 2001, 61, 2530270.). Diseases related to angiogenesis occurring in pathological conditions include

hemangioma; angiofibroma; arteriosclerosis which is a vascular malformation cardiovascular disease; angiostenosis; edematous sclerosis; etc. Eye diseases caused by angiogenesis include corneal transplantation angiogenesis; angiogenic glaucoma; diabetic retinopathy; angiogenic corneal disease; age-related macular degeneration; pterygium; retinal degeneration; retreolental fibroplasias; granular conjunctivitis; etc. Additionally, skin diseases caused by angiogenesis include chronic inflammatory diseases such as arthritis; psoriasis; telangiectasis; granuloma pyogenicum; sebborhoeic dermatitis; acne; etc., and angiogenisis is also related to periodontal disease. In tumors, cancer cells continuously induce new capillary vessels as pathways to receive nutrient and oxygen for growth thereof and discharge of waste material, and thus angiogenisis is indispensable for growth and metastasis of cancer cells.

The process of angiogenesis generally involves decomposition of the basement membrane of blood vessels by protease, formation of vascular lumen by differentiation, proliferation, and migration of endothelial cells, and reconstruction of blood vessels. Protease involved in this process is referred to as matrix metalloproteinase (hereinafter referred to as 'MMP' enzyme).

Matrix metalloproteinase (MMP) is an enzyme secreted from cells such as polymorphonuclear neutrophile, macrophage, fibroblast, and bone cells, etc. MMP is known to decompose protein constituents of the extracellular matrix to be involved in wound healing, angiogenesis, pregnancy, decomposition and reconstruction of connective tissue, etc. Overexpression of MMP is known to

be a main cause of various diseases including invasion and metastasis of tumors, and arthritis, by unwanted decomposition of connective tissue. The enzyme is involved in various diseases such as arthritis, tumor growth and metastasis, periodontal disease, multiple sclerosis, etc.

MMP enzymes are a family of metalloproteinase, having zinc at their active site, and they decompose and reconstruct proteins such as membrane collagen, aggrecan, fibronectin, and laminin that form structural proteins in an extracellular matrix. Functions of the enzyme in organisms are naturally inhibited by intrinsic tissue inhibitors of metalloprotease (TIMPs), but an imbalance thereof causes overexpression and activation of MMPs to cause decomposition of tissue. Functions of MMPs play important roles in the development of chronic diseases such as multiple sclerosis, arthritis, fibrosis and other inflammation, and growth and metastasis of malignant tumors. For this reason, MMPs are attractive targets as inhibitors of development and treatment of such diseases.

Up to now, 17 kinds of MMP enzymes in humans have been known, and they show many similarities therebetween. They are largely divided into collagenase, stromelysin, gelatinase, matrilysin, metalloelastase, and membrane-type (MT) MMP enzymes.

Epileptic enzyme fibroblast collagenase pertains to MMP-1, and substrates of the enzyme thereof are collagen type I, II, III, VII, VIII, X, and gelatin. 72-Kda gelatinase A pertains to MMP-2, and substrates of the enzyme thereof are gelatin, collagen type IV, V, VII, X, elastin, and fibronectin.

Stormelysin-1 pertains to MMP-3, and substrates of the enzyme thereof are proteoglycan, fibronectin, laminin, procolagenase, collagen type IV, V, IX, X, and elastin. Matrilysin pertains to MMP-7, and substrates of the enzyme thereof are proteoglycan, fibronectin, laminin, procolagenase, gelatin, collagen type IV, elastin, and urokinase. Polymorphonuclear leukocyte collagenase pertains to MMP-8, and substrates of the enzyme thereof are the same as those of MMP-1. Stormelysin-2 pertains to MMP-10, and substrates of the enzyme thereof are the same as those of MMP-3. Stormelysin-3 pertains to MMP-11, and substrates of the enzyme thereof are laminin and fibronectin. Macrophage metalloelastase pertains to MMP-12, and substrates of the enzyme thereof are elastin and fibronectin. Up to now, targeted MMPs include MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13, membrane-type-1-MMP (MT1-MMP), etc.

During carcinogenesis, various MMPs are simultaneously produced to be involved in growth and metastasis of tumors. In metastasis of cancer cells, malignant cancer cells are separated from a primary tumor and produced MMPs to decompose main ingredients of extracellular matrices, collagen, fibronectin, proteoglycan, etc., and cause migration and proliferation of endothelial cells. In this process, MMPs such as MMP-1, MMP-2, MMP9, etc. act. Therefore, inhibitors of these MMP enzymes can be used for a novel anticancer drug blocking growth and metastasis of cancer cells. Collagen, which is a constitutional ingredient of the main protein of an extracellular matrix, maintains its structural form in various tissues and provides physical strength,

and is involved in various processes such as cell attachment, migration, differentiation, etc. Turnover of collagen is required for reconstruction of connective tissue during growth and development of cells, and it is involved in arthritis, glomerulonephritis, atherosclerosis, tissue ulceration, periodontal disease, fibrotic lung disease, and pathological processes accompanying invasion and metastasis of cancer cells. Particularly, it has been clarified that during carcinogenesis, in cancer invasion and metastasis stages, MMP-2 and MMP-9 are excessively secreted. MMP-2, which is the enzyme mostly expressed in bodies, decomposes collagen type V, VII, X, fibronectin, elastin, and all forms of unfolded collagen, as well as collagen type IV. Type IV collagenase MMP-2 and MMP-9 decompose type IV collagen, which is a main ingredient of basement membranes, which are the first barrier to cancer metastasis, and they are the most important enzymes involved in invasion and metastasis of cancer cells. Therefore, a type IV collagenase MMP-2 and MMP-9 inhibitor can be used for treatment of cancer invasion and metastasis, and for rheumatoid and periodontal disease, as well as for corneal ulcers caused by decomposition of collagenic connective tissue.

Collagenase that is secreted by fibroblast, polymorphonuclear leukocyte, epithelia, and macrophage cells is an important enzyme in periodontal disease. First, an endotoxin such as lipopolysaccharide is secreted to periodontal tissue due to anaerobic gram negative infection, and thereby tissues are directly destroyed, or cytokines such as interleukin and prostaglandin are secreted because of immunization of bodies, to cause inflammation. Collagen, a matrix

of periodontal tissues, is decomposed by collagenase secreted by stimulation of these inflammation media and bacterial collagenase to cause gingival inflammation, which, if left, progresses toward periodontal disease. In addition, MMP-3 and MMP-8 also reduce proteoglycan, which is a main polymer ingredient of connective tissues. Thus, an inhibitor for these enzymes (MMP-3, MMP-8) can also be used for treating periodontal disease.

Arthritis, a representative inflammatory disease, occurs because of autoimmunization, but as the disease progresses, chronic inflammation occurring in the synovial cavity between articulations causes angiogenesis to destroy connective tissues without blood vessels. With the aid of inflammation-causing cytokine, synovial cells and endothelial cells that proliferate in the synovial cavity progress angiogenesis, thereby forming a connective tissue layer, an articular disc, to destroy connective tissues functioning as a cushion (Koch, A. E. Polverini, P, J., Leibovich, S. J., Arthritis Rheum. 1986, 29, 471. Koch, A. E., Arthritis Rheum. 1998, 41, 951). It has been clarified that MMP enzymes decompose the main ingredients of connective tissue, collagen and proteoglycan (Sapolsky, A. I., Keiser, H., Howell, D. S., Woessner, J. F., Jr. J. Clin. Invest. 1976, 58, 1030). They have been cloned from breast cancer cells, and clarified to be involved in arthritis (Freiji, J. M., Diez-Itza, I., Balbin, M., Sanchez, L. M., Blasco, R., Tolivia, J., Lopez-Otin, C., J. Biol. Chem. 1994, 269, 16766). In addition, the main substrate of MMP-13 is type II collagen which is a main constructional ingredient of articular cartilage, and as it has been clarified that a concentration

of the enzyme increases in human bone and joint tissues and the enzyme is produced by chondrocyte, it has also been clarified to be involvedd in arthritis, and thus an inhibitor for the enzyme can be used for an arthritis-treating agent.

A TNF-α converting enzyme (TACE) catalyzes formation of TNF-α from a membrane-bound TNF-α protein precursor. TNF-α is a pro-inflamatory-cytokine involved in antitumor processes as well as in rheumatoid arthritis, septic shock, transplantation rejection, insulin tolerance, and HIV inflammation; and it is also known to mediate congestive heart failure, cachexia, anorexia, inflammation, fever, inflammatory disease of the central nervous system and inflammatory bowel disease. It has been proven in a study using transfected animals and an antibody for TNF-α that blocking TNF-α formation inhibits progress of arthritis (Rankin, E. C., Choy, E. H., Kassimos, D., Kingsley, G. H., Sopwith, A. M., Isenberg, D. A., Panayi, G. S. Br. J. Rheumatol. 1995, 34, 334). Therefore, a low molecular inhibitor for MMP and TACE is expected to have potential for treating various disease symptoms including arthritis.

Eye diseases causing blindness a few hundred times every year are also caused by angiogenesis (Jeffrey, M. I., Takayuki, A., J. Clin. Invest. 1999, 103, 1231). Diseases such as macular degeneration occurring in old persons, diabetic retinopathy, retinopathy of prematurity, angiogenic glaucoma, and corneal disease of angiogenesis are caused by angiogenesis (Adamin, A. P., Aiello, L. P., D'Amato, R. A., Angiogenesis 1999, 3, 9). Diabetic retinopathy is a complication of diabetes, wherein capillaries in retina infiltrate into the

vitreous body by angiogenesis to cause blindness. Eyes are tissue without blood vessels, and growth of blood vessels causes blindness. Eye disease caused by angiogenesis has no appropriate treating agent, and presently, steroids or antibiotics are used. If the disease is more progressed, blood vessels are cauterized or photocoagulated, but the effects are temporary and cannot block proliferation of blood vessels, and thus the disease relapses. Therefore, the most basic treatment method is to block angiogenesis.

Additionally, psoriasis characterized by red spots and scale on the skin is a chronic proliferatory skin disease, and this is also not easily healed and it involves pain and malformation. For an ordinary person, horny cells(or corneocyte) proliferate once a month, while for a patent with psoriasis, they proliferate at least once a week. For such fast proliferation, a great deal of blood must be supplied, and thus angiogenesis actively occurs (Folkman, J. J. Invest. Dermatol. 1972, 59, 40). Thus, an angiogenesis inhibitor can be used as a novel treating agent of dermatological diseases such psoriasis.

It is known that since the proteinases are involved in various physiological processes such as embryogenesis, tissue formation, salivary gland formation, odontogenesis, etc., they are involved in various diseases of pathological processes such as cancer metastasis, periodontal disease, rheumatoid arthritis, inflammation, hyperparathyroidism, diabetes, corneal ulcers, osteoporosis, stomach ulcers, wounds, wrinkles, acne, AIDS, burns, arteriosclerosis, bone fractures, etc.

MMP inhibitors that can be used for treating agents of various diseases

have been subject to many patents and patent applications, as follows. Specifically, they are described in U.S.P. No. 5,189,178; U.S.P. No. 5,455,258; U.S.P. No. 5,506,242; U.S.P. No. 5,672,615; U.S.P. No. 5,756,545; U.S.P. No. 5,804,593; U.S.P. No. 5,817,822; U.S.P. No. 5,859,061; U.S.P. No. 5,861,510; U.S.P. No. 5,962,471; U.S.P. No. 5,985,900; U.S.P. No. 6,022,873; U.S.P. No. 6,022,893; U.S.P. No. 6,071,903; U.S.P. No. 6,121,272; U.S.P. No. 6,143,744; U.S.P. No. 6,150,394; U.S.P. No. 6,153,612; U.S.P. No. 6,156,798; U.S.P. No. 6,159,995; and U.S.P. No. 6,612, 821.

As explained, through recent studies of MMP inhibitors, efforts to prevent and treat various diseases and pathological processes such as cancer metastasis, periodontal disease, rheumatoid arthritis, inflammation, hyperparathyroidism, diabetes, corneal ulcers, osteoporosis, stomach ulcers, wounds, wrinkles, acne, AIDS, burns, arteriosclerosis, bone fractures, etc. have been extensively made, but satisfactory effects for inhibiting MMP have not been obtained.

SUMMARY OF THE INVENTION

In order to solve the problems of the prior art, it is an object of the present invention to provide novel sulfonamide derivatives having superior enzyme inhibitory activities to the existing matrix metalloproteinase inhibitor by acting as angiogenesis inhibitors.

It is another object of the present invention to provide novel intermediates of the sulfonamide derivatives.

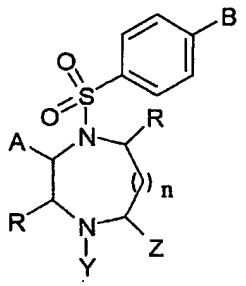
It is another object of the present invention to provide a process for

preparing novel sulfonamide derivatives and intermediates thereof.

It is another object of the present invention to provide a pharmaceutical composition for treating various diseases, acting as a matrix metalloproteinase inhibitor by comprising the sulfonamide derivatives, pharmaceutically acceptable salts, or solvates thereof.

In order to achieve these objects, the present invention provides a compound represented by the following Chemical Formula 1, or optical isomers, pharmaceutically acceptable salts, or solvates thereof:

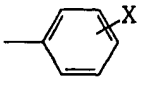
[Chemical Formula 1]



wherein,

n is 0, 1, 2 or 3;

A is CO_2H, CONHOH, CH_2SH, or CH_2OH;

B is hydrogen; a C1-18 alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-

heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group or nitro group); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-9 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound);

R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound;

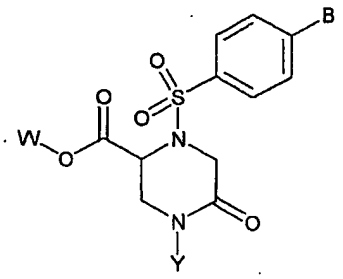
Z is hydrogen, oxygen, or sulfur, and in the case Z is oxygen or sulfur, it takes a double bond; and

Y is hydrogen; a C1-8 lower alkyl group; an aryl group; a heteroaryl; a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound; a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; an amide compound of CONHR or NHCOR; a carbamate of NHCOOR; a urea compound of NHCONHR; a C1-8 lower alkyl group having a double bond or a triple bond; or a C9-20 higher alkyl group having a double bond or a triple bond (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a

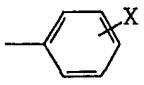
tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by tetragonal to octagonal cyclic compound).

The present invention also provides a process for preparing a compound of the Chemical Formula 1 wherein A is CONHOH, by reacting a compound of the following Chemical Formula 2 with NH_2OH and KOH, or NH_2OH in the presence of $AlCl_3$.

[Chemical Formula 2]



wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-9 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl amine derivative, a C1-20 alkyl carboxylic acid derivative, an amine group, or a nitro group); an amide compound of CONHR or NHCOR;

a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound);

W is hydrogen, or a methyl, ethyl, t-butyl, or C1-8 lower alkyl group comprising a benzyl group; and

Y is hydrogen; a C1-18 alkyl group; an aryl group; a heteroaryl; a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound; a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; a urea compound of NHCONHR; a C1-8 lower alkyl group having a double bond or a triple bond; or a C9-20 higher alkyl group having a double bond or a triple bond (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound).

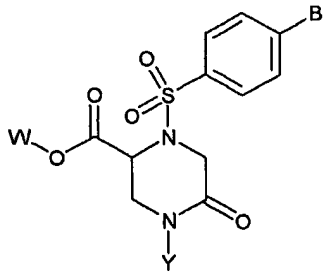
The present invention also provides a process for preparing a compound of the Chemical Formula 1 wherein A is CO_2H, by hydrogenating a compound of the Chemical Formula 2 in the presence of an inorganic base, acid-base, or a Pd/C catalyst.

The present invention also provides a process for preparing a compound of the Chemical Formula 1 wherein A is CH_2OH, by dissolving a compound of the Chemical Formula 2 in methanol, ethanol, or THF, and introducing a reducing agent therein.

The present invention also provides a process for preparing a compound of the Chemical Formula wherein A is CH_2SH, by Mitsunobu-reacting a compound of the Chemical Formula 1, wherein A is CH_2OH, and adding NaOH thereto.

The present invention also provides a compound represented by the following Chemical Formula 2, optical isomers, pharmaceutically acceptable salts, or solvates thereof:

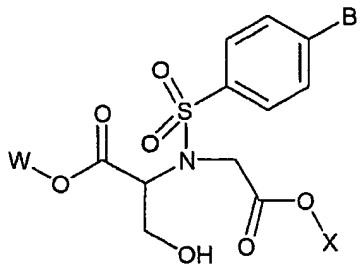
[Chemical Formula 2]



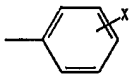
(wherein B, W, and Y are as defined above.)

The present invention also provides a process for preparing a compound represented by the above Chemical Formula 2, by reacting a compound of the following Chemical Formula 3 with methanesulfonyl chloride, toluenesulfonyl chloride, or triflic anhydride in the presence of a base, and reacting it with a primary amine.

[Chemical Formula 3]



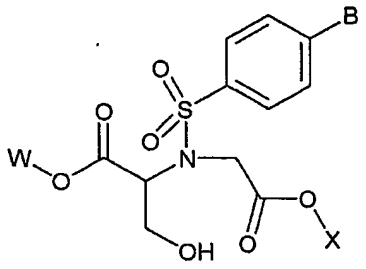
wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-9 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl amine derivative, a C1-20 alkyl carboxylic acid derivative, an amine group, or a nitro group); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound);

W and X are independently or simultaneously hydrogen, or a

methyl, ethyl, t-butyl, or C1-8 lower alkyl group comprising a benzyl group.The present invention also provides a compound represented by the following Chemical Formula 3, optical isomers, pharmaceutically acceptable salts, or solvates thereof:

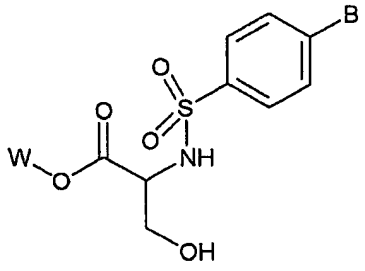
[Chemical Formula 3]



(wherein B, W, and X are as defined above.)

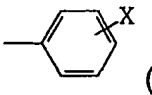
The present invention also provides a process for preparing a compound represented by the above Chemical Formula 3, by reacting a compound of the following Chemical Formula 4 with a halogen compound, an ethyl bromoacetate in the presence of inorganic base, and DMF or acetonitrile solvent.

[Chemical Formula 4]



(wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a

heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound.); and

W is a methyl, ethyl, t-butyl, or C-18 lower alkyl group comprising a benzyl group.)

The present invention also provides a pharmaceutical composition comprising the compound of the Chemical Formula 1, optical isomers, pharmaceutically acceptable salts, or solvates thereof as an active ingredient.

The present invention also provides a method for treating cancer metastasis and solid cancer using the compound of the Chemical Formula 1.

The present invention also provides a method for treating diseases

related to angiogenesis using the compound of the Chemical Formula 1.

DETAILED DESCRIPTION AND THE PREFERRED EMBODIMENTS

The present invention will now be explained in detail.

The present invention relates to sulfonamide derivatives of the above Chemical Formula 1 that can be used as angiogenesis controlling material to inhibit overexpression of matrix metalloproteinase, which decomposes the extracellular matrix of connective tissue and protein constituents of basement membranes, and thus has superior enzyme inhibitory activity to the existing matrix metalloproteinase, and a process for preparing the same.

The compound of the above Chemical Formula 1 according to the present invention is a compound substituted with a phenyl sulfonyl group at position 4, and it is used as an angiogenesis controlling material to show superior angiogenesis inhibiting activity.

The compound of the present invention is preferably a compound of the Chemical Formula 1, wherein A is CONHOH.

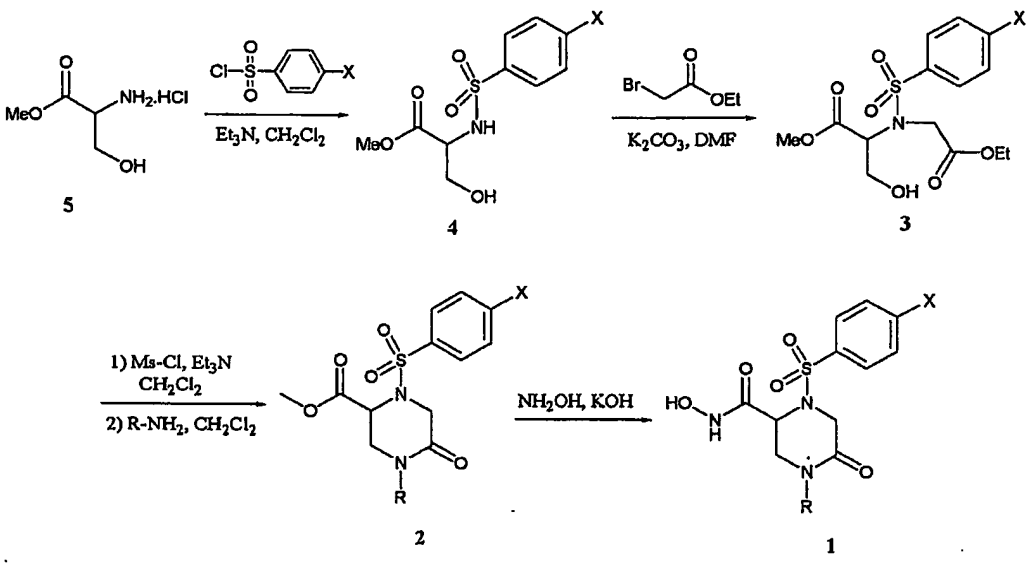
Additionally, the compound of the present invention is preferably a compound of the Chemical Formula 1, wherein A is CO_2H.

Additionally, the compound of the present invention is preferably a compound of the Chemical Formula 1, wherein A is CH_2SH.

Additionally, the compound of the present invention is preferably a compound of the Chemical Formula 1, wherein A is CH_2OH.

A process for preparing the compound of the Chemical Formula 1, wherein A is CONHOH is as shown in the following scheme 1.

[Scheme 1]



As shown in scheme 1, an amino acid derivative of the Chemical Formula 5 such as D-serine methyl ester HCl or D-threonine methyl ester HCl is treated with benzenesulfonyl chloride in a solution comprising 2 equivalents of Et_3N and a catalytic amount of 4-dimethylaminopyridine, to prepare a compound of the Chemical Formula 4.

Then, the compound of the Chemical Formula 4 is dissolved in a solvent such as DMF or acetonitrile, an inorganic base such as potassium carbonate is introduced therein, and it is reacted with ethylbromoacetate to prepare a compound of the Chemical Formula 3. More preferably, the compound of the Chemical Formula 4 is reacted with ethylbromoacetate in a solvent such as DMF or acetonitrile in which an inorganic salt such as potassium carbonate and a catalytic amount of Et_3N is introduced to prepare a compound of the Chemical Formula 3. According to the above process,

the process time can be reduced, and the yield can be greatly increased. In a solvent such as DMF or acetonitrile, using 1.5 to 3 equivalents of potassium carbonate and a catalytic amount of Et_3N, the reaction is conducted at 25 to 90 ℃ for 3 to 8 hours to greatly improve the yield to 65 to 85% compared to the case of using only potassium carbonate.

Additionally, in a solvent such as DMF or acetonitrile, a compound having an appropriate alcohol protection group such as trimethylsilyl, an inorganic salt such as potassium carbonate, and a catalytic amount of Et_3N are introduced, and an alcohol group of the compound of the Chemical Formula 4 is reacted with ethylbromoacetate to prepare a compound of the Chemical Formula 3b having an alcohol protection group. The compound having an alcohol protection group includes, in addition to the above-mentioned trimethylsilyl, a lower alkyl; a substituted methyl, ethyl, or benzyl ether such as methoxy methyl, 1-ethoxyethyl, or p-methoxybenzyl; an ester such as formate, acetate, etc.; and a carbonate such as methylcarbonate, etc.

Then, the compound of the Chemical Formula 3 is reacted with a compound that increases the reactivity of the alcohol group such as methanesulfonyl chloride, toluenesulfonyl chloride, or triflic anhydride in a dichloromethane solvent in which a base such as Et_3N is introduced, and it is reacted with various agents having a primary amine group such as ammonia or methylamine in an appropriate solvent such as dioxane in which a base such as Et_3N is introduced, to prepare a compound 2.

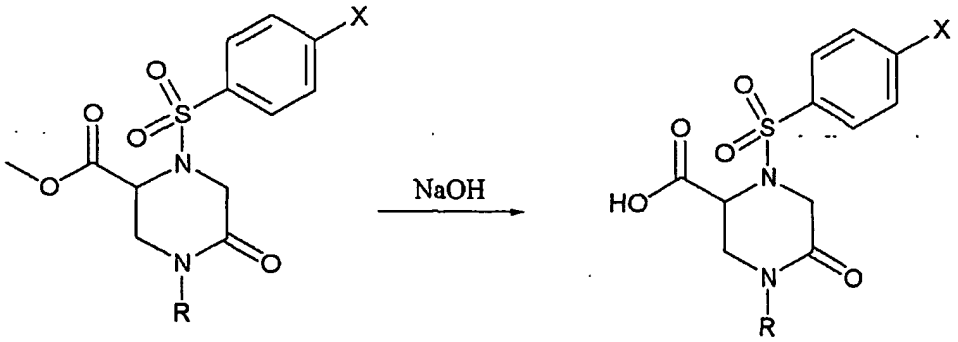
In addition, in the case of a compound of the Chemical Formula 3

having an alcohol protection group, the alcohol protection group is removed, and then the compound is reacted with a compound that increases reactivity of the alcohol group such as methanesulfonyl chloride, toluenesulfonyl chloride, or triflic anhydride in the presence of a base such as Et_3N in a dichloromethane solvent, and it is then reacted with various agents having a free amine group such as ammonia in an appropriate solvent such as dioxane in the presence of base such as Et_3N, to prepare a compound 2.

Then, the compound 2 is dissolved in 1.7 M of a methanol solution of hydroxylamine (NH_2OH) (prepared from hydroxylamine and potassium hydroxide (KOH) according to Fieser and Fieser, Vol. 1, p. 478 process) to prepare a compound of the Chemical Formula 1. Instead of the methanol solution of hydroxylamine, hydroxylamine (NH_2OH) and a metal compound such as aluminum chloride ($AlCl_3$) can be used.

In addition, a process for preparing a compound of the Chemical Formula 1 wherein A is CO_2H is as shown in the following Scheme 2.

[Scheme 2]

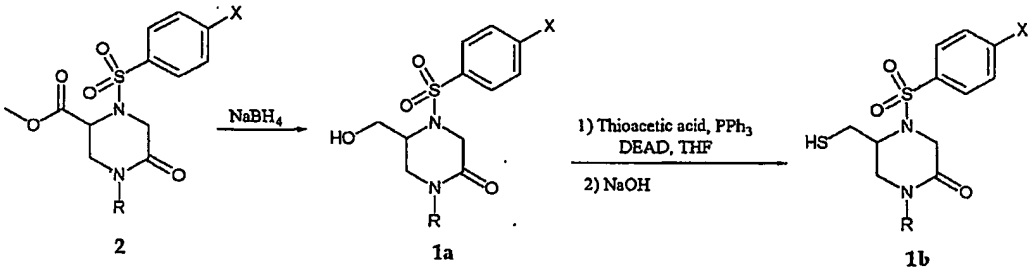


2 1

As shown in the scheme 2, the compound 2 is dissolved in a solvent such as methanol, ethanol, or THF and it is reacted with NaOH, potassium hydroxide (KOH), LiOH, or $Ba(OH)_2$ to prepare a compound of the Chemical Formula 1, wherein A is CO_2H.

In addition, a process for preparing a compound of the Chemical Formula 1 wherein A is CH_2SH is as shown in the following Scheme 3.

[Scheme 3]

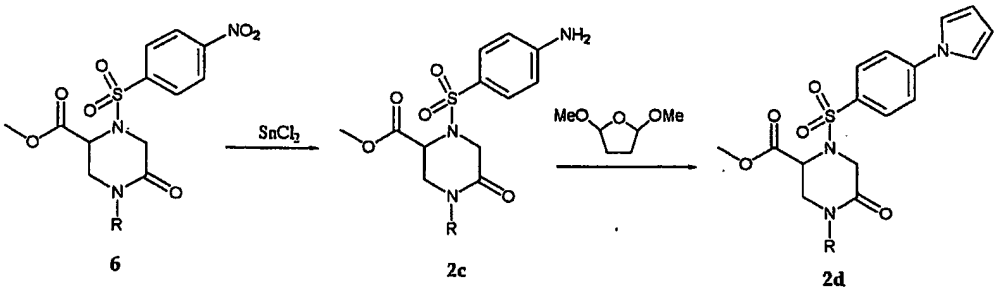


2 1a 1b

As shown in the sheme 3, the compound 2 is dissolved in methanol, ethanol, or a THF solvent, and an ester group of the compound 2 is converted into an alcohol group using a reducing agent such as $NaBH_4$ to prepare a compound of the Chemical Formula 1a. Then, the compound 1a is converted into a thioester using thioacetic acid by a Mitsunobu reaction, and NaOH is added thereto to prepare a compound of the Chemical Formula 1b, i.e., a compound of the Chemical Formula 1 wherein A is CH_2SH.

In addition, in the case B when the compound of the Chemical Formula 1 forms a pyrrole ring, a process for preparing the compound of the Chemical Formula 1 is as shown in Scheme 4.

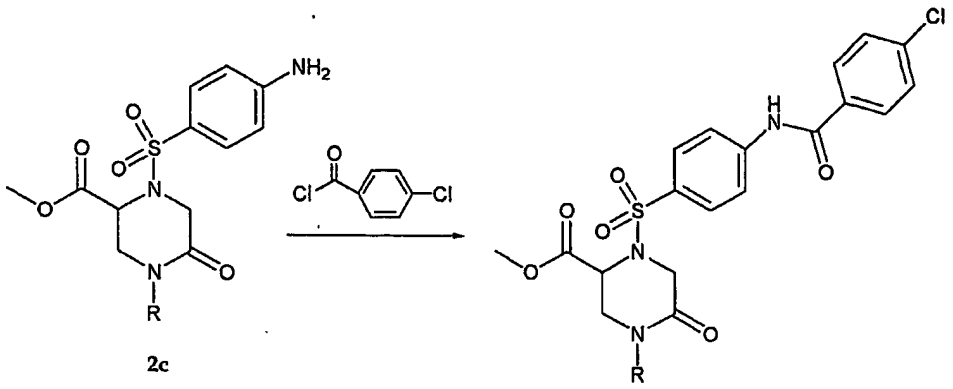
[Scheme 4]



As shown in the Scheme 4, a compound 6 having a 4-nitrobenzenesulfonyl group is hydrogenated using $SnCl_2$ or in the presence of a metal catalyst such as Pd/C, to prepare a compound 2c. Then, the compound 2c is condensed with 2,5-dimethoxytetrahydrofuran to prepare a compound 2d. The present invention is a compound of the Chemical Formula 1 wherein B forms a pyrrole ring prepared by the same reaction as used in the Equations 1, 2, and 3 using the compound 2c.

In addition, in the case of a compound of the Chemical Formula 1 wherein B has an amide group, a process for preparing the same is as shown in Scheme 5.

[Scheme 5]



2c 2f

As shown in the Scheme 5, the compound 2c is reacted with 4-chlorobenzoyl chloride in the presence of Et_3N to prepare a compound 2f. Then, from the compound 2f, a compound of the Chemical Formula 1 wherein B has an amide group is prepared using the same reaction as used in the Schemes 1, 2, and 3.

The present invention also provides a pharmaceutical composition comprising the compound of the Chemical Formula 1, optical isomers, and pharmaceutically acceptable salts or solvates thereof as an active ingredient.

In the pharmaceutical composition of the present invention, the contents of the compound of the Chemical Formula 1 can be controlled according to the purpose of its use, and they are not specifically limited. The pharmaceutical composition of the present invention can be administrated to a patient by oral or non-oral administration in any form, including solid or liquid. The pharmaceutical composition of the present invention may further comprise a pharmaceutically acceptable liquid or solid carrier.

The solid preparation includes a powder, a tablet, dispersable granules or a capsule, and a solid dosage form suitable for oral administration includes a tablet, a powder, or a capsule. An appropriate excipient includes a diluent, a flavoring agent, a solubilizer, a lubricant, a suspension, a binder, and/or a bulking agent. In the case of a powder or capsule, a vehicle can comprise 5 to 70%, and preferably 10 to 70% of the powdered active ingredient. A suitable solid vehicle or excipient includes corn starch, magnesium stearate, film, polyethyleneglycol, talc, sugar, lactose, pectin, dextrin, starch, gelatin, hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose, titan dixode, a low melting point wax, cocoa butter, etc.

The liquid preparation may be a solution, a suspension, or an emulsion. As examples, in the case of a non-oral injection solution, water or a mixed solution of water and propyleneglycol can be used, and the solution is prepared so that its isotonicity, pH etc. are suitable for a living body system. A liquid phase preparation may also be formed of a polyethylene glycol aqueous solution. An aqueous solution suitable for oral administration can be prepared by dissolving an active ingredient in water and adding an appropriate flavoring agent, coloring agent, stabilizer, and thickener. An aqueous suspension suitable for oral administration can be prepared by dispersing the powdered active ingredient in a viscous material such as natural or synthetic gum, resin, methylcellulose, sodium carboxymethylcellulose, or other known suspensions.

A preferable pharmaceutical preparation is a unit dosage form. The preparation is finely divided into a unit administration form comprising an

appropriate amount of active ingredient. The unit dosage form can be a packaged preparation comprising a separated amount of the preparation, for example a packaged tablet or capsule, or a powder in a vial or ampule.

As explained, the pharmaceutical composition of the present invention comprising the compound of the Chemical Formula 1 as an active ingredient acts as a superior matrix metalloproteinase inhibitor and can be used for a treating agent of various diseases and pathological processes such as cancer metastasis, periodontal disease, rheumatoid arthritis, inflammation, hyperparathyroidism, diabetes, corneal ulcers, osteoporosis, stomach ulcers, wounds, wrinkles, acne, AIDS, burns, arteriosclerosis, bone fractures, etc. The pharmaceutical composition comprising the compound of the Chemical Formula 1 is preferably an anticancer drug.

The present invention will be explained in more detail with reference to the following Examples. However, these are to illustrate the present invention, and the present invention is not limited to them.

Example 1: Synthesis of methyl 3-hydroxy-2-(4-methoxy-benzenesulfonylamino)propionate

DL-serine methylester HCl (14,6 g, 93,8 mmol) of the Chemical Formula 5 was suspended in 400 mL of dichloromethane, and Et_3N (29 Ml, 206 mmol) and a catalytic amount of 4-dimethylaminopyridine were introduced therein while maintaining the temperature at 0 ℃, and 4-methoxybenzene-sulfonyl chloride (19.2 g 94 mmol) was add dropwise. They were stirred at room temperature for 20 hours, washed with 200 mL of distilled water, dried, and

concentrated under reduced pressure to obtain a yellow solid title compound (26.5 g, yield 97%).

Example 2: Synthesis of methyl 2-[ethoxycarbonylmethyl-(4-methoxy-benzenesulfonyl)-amino]-3-hydroxy-propionate

The compound of Example 1 (7.2 g, 24.8 mmol) and anhydrous potassium carbonate (7 g, 50 mmol) were suspended in DMF (50 mL), and ethyl bromoacetate (4.5 Ml, 37 mmol) was added dropwise. After stirring for 40 hours, 50 ml of distilled water and 100 mL of ethyl acetated were introduced and stirred to separate layers. The supernatant was washed with a 1N HCl aqueous solution (50 mL), a saturated $NaHCO_3$ aqueous solution (50 mL), and distilled water (100 mL), and it was dried and concentrated under reduced pressure. The mixture was separated using hexane and ethylacetate (2:1) in a silica gel column to obtain a yellow thick oily title compound (5.04 g , yield 54%).

^1H NMR ($CDCl_3$, 400MHz) δ 1.28(m, 3H), 3.58(s, 3H), 3.63(m, 1H), 3.85(s, 3H), 3.96(d, J=18.8Hz, 1H), 4.09(m, 1H), 4.23(m, 2H), 4.41(d, J=18.8Hz, 1H), 4.73(dd, J=9.5, 4.2Hz, 1H), 6.96(d, J=8.8Hz, 2H), 7.77(d, J=8.8Hz, 2H).

Example 3: Synthesis of methyl 2-[ethoxycarbonylmethyl-(4-methoxy-benzenesulfonyl)-amino]3-hydroxy-propionate

The compound of Example 1 (5.65 g, 19.5 mmol) and anhydrous potassium carbonate anhydrous (8 g, 60 mmol) were suspended in DMF (35 mL), a catalytic amount of Et_3N was introduced, and ethyl bromoacetate (4.3 mL, 40 mmol) was added dropwise. After stirring for 5 hours, 50 mL of

distilled water and 100 mL of ethyl acetate were introduced and stirred to separate layers. The supernatant was washed with a 1N HCl aqueous solution (50 mL), a saturated $NaHCO_3$ aqueous solution (50 mL), and distilled water (100 mL), and it was dried and concentrated under reduced pressure. The mixture was separated using hexane and ethylacetate (2:1) in a silica gel column to obtain a yellow thick oily title compound (5.26 g, yield 72%).

^1H NMR ($CDCl_3$, 400MHz) δ 1.28(m, 3H), 3.58(s, 3H), 3.63(m, 1H), 3.85(s, 3H), 3.96(d, J=18.8Hz, 1H), 4.09(m, 1H), 4.23(m, 2H), 4.41(d, J=18.8Hz, 1H), 4.73(dd, J=9.5, 4.2Hz, 1H), 6.96(d, J=8.8Hz, 2H), 7.77(d, J=8.8Hz, 2H)

Example 4: Synthesis of methyl 1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-carboxylate

The compound of Example 3 (1.97 f , 6.0 mmol) was suspended in 50 mL of dichloromethane, and Et_3N (1.2 Ml, 8.4 mmol) and methane sulfonyl chloride (0.56 mL, 7.2 mmol) were added while maintaining the temperature at 0 ℃. After stirring at room temperature for 16 hours, the reactant was washed with 50 mL of distilled water, and it was dried and distilled under reduced pressure. It was dissolved in 15 mL of 1,4-dioxnae, and Et_3N (1.6 mL, 12 mmol) and 28% ammonia water (0.73 mL, 1 mmol) were added. After stirring for 24 hours, 50 mL of distilled water and 100 mL of ethyl acetate were introduced, and the layers were separated. The supernatant was collected and dried, concentrated under reduced pressure, and separated in a silica gel column to obtain a yellow oily title compound 4a (0.75 g, yield 38%).

^1H NMR ($CDCl_3$, 400MHz) δ 3.57(s, 3H), 3.72(t, J=3.1Hz, 1H), 3.87(s,

3H), 3.92(d, J=17.3Hz, 1H), 4.21(d, J=17.1Hz, 1H), 4.86(t, J=3.3Hz, 1H), 6.31(br, 1H), 6.99(dd, J=7.1, 1.9Hz, 2H), 7.73(dd, J=6.8, 2.0Hz, 2H)

Example 5: Synthesis of 1-(4-Methoxy-benzenesulfonyl)-5-oxo-piperazine-2-hydroxamate)

To the compound of Example 4 (0.49 g, 1.49 mmol), 10 mL of a 1.7 M hydroxylamine (H_2NOH) solution (prepared from hydroxylamine and potassium hydroxide (KOH) according to Fieser and Fieser, Vol. 1, p 478 method) was added and stirred for 5 hours. After 5 hours, the reactant was acidified with a 2 N HCl aqueous solution and the pH was made neutral with a saturated $NaHCO_3$ aqueous solution, and then it was extracted with ethyl acetate, and dried and concentrated under reduced pressure. The reactant was dissolved with ethyl acetate and methanol (MeOH), and then hexane was added thereto to obtain a white solid title compound (0.22 g, yield 45%) by recrystallization.

^1H NMR (DMSO-d_6, 400MHz) δ 3.20(m, 2H), 3.72(t, J=3.1Hz, 1H), 3.83(s, 3H), 3.88(br d, 1H), 4.09(s, 1H), 4.32(s, 1H), 7.09(d, J=8.8Hz, 2H), 7.73(d, J=8.8Hz, 1H), 7.96(s, 1H), 8.99(br, 1H), 10.78(br, 1H)

Example 6: Synthesis of methyl 4-benzyl-1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that the compound of Example 3 and benzylamine were used.

^1H NMR ($CDCl_3$, 400MHz) δ 3.33(s, 3H), 3.52(dd, J=12.5, 1.9Hz, 1H), 3.66(dd, J=12.6, 4.6Hz, 1H), 3.87(s, 3H), 4.04(d, J=17.1Hz, 1H), 4.18(d, J=14.6Hz, 1H), 4.27(d, J=17.1Hz, 1H), 4.78(d, J=4.6Hz, 1H), 4.87(d, J=14.6Hz,

1H), 6.97(d, J=9.0Hz, 2H), 7.13(m, 2H), 7.28(m, 3H), 7.71(dd, J=7.1, 1.9Hz, 1H)

Example 7: Synthesis of 4-Benzyl-1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-hydroxamate

A title compound was prepared by the same method as in Example 5, except the compound of Example 6 was used.

^{1}H NMR (DMSO-d_6, 400MHz) δ 3.23(dd, J=13.2, 5.3Hz, 1H), 3.33(dd, J=12.6, 3.9Hz, 1H), 3.84(s, 3H), 4.08(m, 3H), 4.34(t, 1H), 4.58(d, J=15.1Hz, 1H), 6.95(m, 2H), 7.09(d, J=9.0Hz, 2H), 7.23(m, 3H), 7.74(d, J=8.8Hz, 2H), 8.99(br, 1H), 10.85(s, 1H)

Example 8: Synthesis of Methyl 1-(4-methoxy-benzenesulfonyl)-5-oxo-4-(2-piperidin-1-yl-ethyl)-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that a yellow oily title compound (yield 83%) was prepared using the compound of Example 3 and 1-(2-aminoethyl)piperidine(1-(2-aminoethyl)piperidine).

^{1}H NMR ($CDCl_3$, 400MHz) δ 1.41(m, 2H), 1.51(m, 4H), 2.36(m, 6H), 3.43(t, J=6.6Hz, 2H), 3.54(s, 3H), 3.77(dd, J=12.4, 2.2Hz, 1H), 3.83(dd, J=12.6, 4.6Hz, 1H), 3.87(s, 3H), 3.90(d, J=17.1Hz, 1H), 4.17(d, J=16.8Hz, 1H), 4.82(s, 1H), 6.98(d, J=8.8Hz, 2H), 7.72(d, J=8.8Hz, 2H)

Example 9: Synthesis of 1-(4-Methoxy-benzenesulfonyl)-5-oxo-4-(2-piperidin-1-yl-ethyl)-piperazine-2-hydroxamate hydrochloride

A title compound was prepared by the same method as in Example 5,

except that it was prepared from the compound of Example 8 and then treated with HCl, and recrystallized with MeOH/ether to obtain a light yellow solid (yield 31%).

^{1}H NMR ($CDCl_3$, 400MHz)δ 1.42(br s, 2H), 1.56(m, 4H), 2.42(br m, 6H), 3.48(t, J=6.6Hz, 2H), 3.65-3.82(br m, 2H), 3.85(s, 3H), 4.00-4.14(m, 2H), 4.62(br s, 1H), 6.98(d, J=8.3Hz, 2H), 7.72(d, J=8.6Hz, 2H), 9.21(br, 1H)

Example 10: Synthesis of Methyl 1-(4-methoxy-benzenesulfonyl)-4-(2-morpholin-4-yl-ethyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that the compound of Example 3 and N-(2-aminoethyl)morpholine were used to prepare a yellow oil (yield 74%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 2.43(m, 6H), 3.45(m, 2H), 3.53(s, 3H), 3.64(m, 3H), 3.75(m 1H), 3.82(m, 1H), 3.87(s, 3H), 3.90(d, J=17.1Hz, 1H), 4.17(d, J=16.8Hz, 1H), 4.84(s, 1H), 6.99(d, J=9.0Hz, 2H), 7.73(d, J=8.8Hz, 2H)

Example 11: Synthesis of 1-(4-Methoxy-benzenesulfonyl)-4-(2-morpholin-4-yl-ethyl)-5-oxo-piperazine-2-hydroxamate hydrochloride

A title compound was prepared by the same method as in Example 5, except that it was prepared from the compound of Example 10 and treated with HCl, and recrystallized with MeOH/ether to obtain a white solid.

Example 12: Synthesis of Methyl 1-(4-methoxy-benzenesulfonyl)-5-oxo-4-pyridin-2-yl-methyl-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that it was prepared from the compound of Example 3 and 2-

aminomethylpyridine, and recrystallized with ethylacetate/hexane to obtain a white solid (yield 85%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 3.41(s, 3H), 3.75-3.90(m, 2H), 3.91(s, 3H), 4.03(d, J=17.1Hz, 1H), 4.26(d, J=17.1Hz, 1H), 4.46(d, J=3.2Hz, 1H), 4.82(m, 1H), 4.84(s, 1H), 6.97(d, J=9.0Hz, 2H), 7.17(m, 2H), 7.62(m, 1H), 7.72(d, J=9.0Hz, 2H), 8.49(s, 1H)

Example 13: Synthesis of 1-(4-Methoxy-benzenesulfonyl)-5-oxo-4-pyridin-2-yl-methyl-piperazine-2-hydroxamate hydrochloride

A title compound was prepared by the same method as in Example 5, except that it was prepared from the compound of Example 12 and treated with HCl, and recrystallized with MeOH/ether to obtain a white solid (yield 48%).

Example 14: Synthesis of Methyl 1-(4-methoxy-benzenesulfonyl)-5-oxo-4-(2-pyridin-2-yl-ethyl)-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that the compound of Example 3 and 2-(2-aminoethyl)pyridine were used to prepare an oil (yield 74%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 2.94(m, 2H), 3.49(s, 3H), 3.69(t, 2H), 3.74(t, J=7.3Hz, 2H), 3.87(s, 3H), 3.89(d, J=17.1Hz, 1H), 4.14(d, J=16.8Hz, 1H), 4.79(t, J=3.7, 2.9Hz, 1H), 6.98(d, J=8.8Hz, 2H), 7.14(t, 2H), 7.59(td, J=7.6, 1.7Hz, 1H), 7.72(d, J=8.6Hz, 2H), 8.49(d, J=4.9Hz, 1H)

Example 15: Synthesis of 1-(4-Methoxy-benzenesulfonyl)-5-oxo-4-(2-pyridin-2-yl-ethyl-piperazine-2-hydroxamate

A title compound was prepared by the same method as in Example 5,

except that it was prepared from the compound of Example 14, and recrystallized with ethyl acetate/hexane to obtain a brown title compound (yield 29%).

Example 16: Synthesis of Methyl 4-cyclopropyl-1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that it was prepared from the compound of Example 3 and cyclopropylamine, and recrystallized with ethylacetate/hexane to obtain a white solid compound (yield 43%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.46(m, 1H), 0.58(m, 1H), 0.77(m, 1H), 0.85(m, 1H), 2.62 (m, 1H), 3.56(s, 3H), 3.67(m, 2H), 3.83-3.87(m, 1H), 3.88(s, 3H), 4.12-4.18(m, 1H), 4.82(m, 1H), 6.99(m, 2H), 7.72(m, 2H)

Example 17: Synthesis of 4-Cyclopropyl-1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-hydroxamate

A title compound was prepared by the same method as in Example 5, except that it was prepared from the compound of Example 16, and recrystallized with ethylacetate/MeOH/hexane to obtain a white solid compound (yield 49%).

Example 18: Synthesis of Methyl 4-butyl-1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that the compound of Example 3 and n-butylamine were used to prepare an oily title compound (yield 80%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.88(t, J=7.3Hz, 3H), 1.24(m, 2H), 1.40(m, 2H), 3.20(m, 1H), 3.45(m, 1H), 3.55(s, 3H), 3.64(dd, J=12.7, 2.2Hz, 1H), 3.72(dd, J=12.7, 4.4Hz, 1H), 3.87(s, 3H), 3.89(d, J=16.3Hz, 1H), 4.16(d, J=16.8Hz, 1H), 4.86(dd, J=4.4, 2.2Hz, 1H), 6.99(d, J=9.7Hz, 2H), 7.73(d, J=8.8Hz, 2H)

Example 19: Synthesis of 4-Butyl-1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-hydroxamate

A title compound was prepared by the same method as in Example 5, except that it was prepared from the compound of Example 18, and recrystallized with CH_2Cl_2 to obtain a white title compound (yield 51%).

^{1}H NMR (DMSO-d_6, 400MHz) δ 0.76(m, 3H), 0.97-1.19(m, 2H), 2.91(m, 1H), 3.22(m, 1H), 3.29-3.41(m, 2H), 3.83(s, 3H), 3.86(d, J=16.6Hz, 1H), 3.95(d, J=16.8Hz, 1H), 4.32(t, J=4.5Hz, 1H), 7.10(d, J=9.0Hz, 2H), 7.74(d, J=8.8Hz, 2H), 8.99(s, 1H), 10.86(s, 1H)

Example 20: Synthesis of Methyl 4-allyl-1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that the compound of Example 3 was used to prepare an oily compound (yield 84%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 3.55(s, 3H), 3.62(dd, J=12.7, 2.2Hz, 1H), 3.69(dd, J=12.7, 4.6Hz, 1H), 3.79(dd, J=15.1, 6.6Hz, 1H), 3.88(s, 3H), 3.93(d, J=17.1Hz, 1H), 4.12(dd, J=14.8, 5.9Hz, 1H), 4.20(d, J=16.8Hz, 1H), 4.86(dd, J=4.6, 2.2Hz, 1H), 5.13(dd, J=17.1, 1.4Hz, 1H), 5.19(dd, J=10.1, 1.1Hz, 1H),

5.58(m, 1H), 6.99(d, J=9.1Hz, 2H), 7.73(d, J=9.0Hz, 2H)

Example 21: Synthesis of 4-Allyl-1-(4-methoxy-benzenesulfonyl)-5-oxo-piperazine-2-hydroxamate

A title compound was prepared by the same method as in Example 5, except that it was prepared from the compound of Example 20 and recrystallized with $CHCl_3$ to obtain a white solid (yield 66%).

Example 22: Synthesis of Methyl 1-(4-methoxy-benzenesulfonyl)-5-oxo-4-prop-2-ynyl-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that it was prepared from the compound of Example 3 and propargylamine, and recrystallized with CH_3Cl/hexane to obtain a white solid (yield 90%).

^1H NMR ($CDCl_3$, 400MHz) δ 2.16(s, 1H), 3.49(s, 3H), 3.72(dd, J=12.5, 4.6Hz, 1H), 3.69(dd, J=12.7, 2.2Hz, 1H), 3.81(s, 3H), 3.86(d, J=17.1Hz, 1H), 4.06(dd, J=17.3, 2.4Hz, 1H), 4.14(d, J=17.1Hz, 1H), 4.19(dd, J=17.6, 2.4Hz, 1H), 4.84(dd, J=4.5, 2.0Hz, 1H), 6.92(d, J=9.0Hz, 2H), 7.66(d, J=9.0Hz, 2H)

Example 23: Synthesis of 1-(4-Methoxy-benzenesulfonyl)-5-oxo-4-prop-2-ynyl-piperazine-2-hydroxamate

A title compound was prepared by the same method as in Example 5, except that it was prepared from the compound of Example 22, and recrystallized with ethylacetate/hexane to obtain a white crystal (yield 35%).

Example 24: Synthesis of Methyl 1-(4-methoxy-benzenesulfonyl)-4-methyl-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 4, except that it was prepared from the compound of Example 3 and methylamine, and recrystallized with ethylacetate/hexane to obtain a white solid (yield 73%)

^{1}H NMR ($CDCl_3$, 400MHz) δ 2.94(s, 3H), 3.57(s, 3H), 3.64(dd, J=12.4, 1.8Hz, 1H), 3.77(dd, J=12.7, 4.8Hz, 1H), 3.87(d, J=16.8Hz, 1H), 3.88(s, 3H), 4.17(d, J=16.8Hz, 1H), 4.87(dd, J=4.6, 1.6Hz, 1H), 6.98(d, J=11.9Hz, 2H), 7.73(d, J=9.0Hz, 2H)

Example 25: Synthesis of 1-(4-Methoxy-benzenesulfonyl)-4-methyl-5-oxo-piperazine-2-hydroxamate

A title compound was prepared by the same method as in Example 5, except that it was prepared from the compound of Example 24, and recrystallized with ethylacetate/MeOH/hexane to obtain a white solid (yield 52%).

^{1}H NMR (DMSO-d_6, 400MHz) δ 2.67(s, 3H), 3.39(m, 2H), 3.82(d, J=16.4Hz, 1H), 3.84(s, 3H), 3.93(d, J=16.4Hz, 1H), 4.42(t, J=4.0Hz, 1H), 7.10(d, J=9.0Hz, 2H), 7.74(d, J=9.0Hz, 2H), 8.98(s, 1H), 10.82(s, 1H)

Example 26: Synthesis of 4-Butyl-1-(4-methoxy-benzenesulfonyl)- 5-oxo-piperazine-2-carboxylic acid

The compound of Example 18 (0.6 g, 1.56 mmol) was dissolved in 8 mL of methanol, and 2 ml of 2N NaOH were added dropwise while maintaining the temperature at 0 ℃. After stirring at room temperature for 6 hours, 20 mL of distilled water were added, and it was extracted with ethyl ether. A 2N HCl solution was added to control the pH of the aqueous solution layer to 1-2, and

then the reactant was extracted with ethylacetate. The supernatant was collected, and dried and concentrated under reduced pressure, and then recrystallized with ethylacetate/hexane to obtain a light yellow solid compound (0.51 g, yield 88%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.86(t, 3H), 1.20(m, 2H), 1.39(m, 2H), 3.27(m, 1H), 3.34(m, 1H), 3.68(d, J=3.2Hz, 2H), 3.86(s, 3H), 3.93(d, J=17.3Hz, 1H), 4.17(d, J=17.3Hz, 1H), 4.84(t, J=3.2Hz, 1H), 6.97(d, J=9.0Hz, 2H), 7.74(d, J=8.8Hz, 2H)

Example 27: Synthesis of 1-Cyclopropyl-5-hydroxymethyl-4-(4-methoxy-benzenesulfonyl)-5-oxo-piperazin-2-one

The compound of Example 16 (1.13 g, 3.06 mmol) was dissolved in 10 mL of methanol, and $NaBH_4$ (0.35 g, 10.8 mmol) was added dropwise while maintaining the temperature at 0 ℃. After stirring at room temperature for 16 hours, 20 mL of distilled water were added and the reactant was concentrated under reduced pressure. Ethyl acetate was added to the aqueous solution layer, the organic layer was dried and concentrated under reduced pressure, and then it was recrystallized with ethylacetate/hexane to obtain a white solid compound (0.56 g, yield 54%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.24(m, 1H), 0.31(m, 1H), 0.70(m, 2H), 2.50(m, 1H), 3.27(dd, J=13.4, 5.6Hz, 1H), 3.38(dd, J=13.2, 5.6Hz, 1H), 3.66(dd, J=10.9, 6.8Hz, 1H), 3.75(dd, J=11.2, 5.2Hz, 1H), 3.80(d, J=17.3Hz, 1H), 3.88(s, 3H), 4.08(dd, J=17.1Hz, 1H), 6.99(d, J=8.8Hz, 2H), 7.73(d, J=8.8Hz, 2H)

Example 28: Synthesis of 1-Cyclopropyl-5-mercaptomethyl-4-(4-

methoxy-benzenesulfonyl)-5-oxo-piperazin-2-one

The compound of Example 27 (0.62 g, 1.82 mmol) was dissolved in 25 mL of THF, and PPh_3 (0.59 g, 2.2 mmol) and thiolacetic acid (0.16 mL, 2.2 mmol) were added dropwise while maintaining the temperature at 0 ℃, and then diethylazodicarboxylate (0.38 mL, 2.2 mmol) was added. After stirring at room temperature for 16 hours, 20 mL of distilled water were added and it was concentrated under reduced pressure. Ethylacetate was added to the aqueous solution layer, and the organic layer was dried and concentrated under reduced pressure. 15 mL of methanol was dissolved therein and 2 mL of 2N NaOH were added dropwise while maintaining the temperature at 0 ℃. After stirring at room temperature for 6 hours, 20 mL of distilled water were added and the reactant was extracted with ethyl acetate. The supernatant was collected, and dried and concentrated under reduced pressure, and then it was recrystallized with ethyl acetate/hexane to obtain a light yellow solid (0.10 g, yield 15%).

^1H NMR ($CDCl_3$, 400MHz) δ 0.27(m, 1H), 0.36(m, 1H), 0.81 (m, 2H), 2.47(m, 1H), 3.31(br, 1H), 3.38(br, 1H), 3.73(m, 2H), 3.80(d, J=17.1Hz, 1H), 3.88(s, 3H), 4.08(dd, J=16.8Hz, 1H), 6.95(d, J=8.8Hz, 2H), 7.75(d, J=8.8Hz, 2H)

Example 29: Synthesis of Methyl 2-(4'-bromo-biphenyl-4-sulfonylamino)-3-hydroxy-propionate

D-serine methylester· HCl of the Chemical Formula 5 (5.62 g, 36.1 mmol) was suspended in 130 mL of dichloromethane, and Et_3N (11 Ml,

76.5 mmol) and a catalytic amount of 4-dimethylaminopyridine were added while maintaining the temperature at 0 ℃, and 4-bromobiphenyl sulfonyl chloride (12.0 g, 36.2 mmol) were added dropwise. After stirring at room temperature for 20 hours, the reactant was washed with a 1N HCl aqueous solution (50 mL), a saturated $NaHCO_3$ aqueous solution (50 mL), and distilled water (100 mL), and it was dried and concentrated under reduced pressure to obtain a white solid title compound (14.0 g, yield 93%).

^1H NMR ($CDCl_3$, 400MHz) δ 3.57(s, 3H), 3.86(dd, J=3.7, 1.7Hz, 1H), 3.89(dd, J=3.6, 1.7Hz, 1H), 4.05(m, 1H), 7.47(d, J=8.0Hz, 2H), 7.60(d, J=8.3Hz, 2H), 7.67(d, J=8.3Hz, 2H), 7.91(d, J=8.0Hz, 2H)

Example 30: Synthesis of Methyl 2-[(4'-bromo-biphenyl-4-sulfonylamino)-[ethoxycarbonylmethyl-amino]-3-hydroxy-propionate

The compound of Example 29 (1.72 g, 4.15 mmol) and potassium carbonate anhydride (1.7 g, 12.4 mmol) were suspended in DMF (10 Ml), and then a catalytic amount of Et_3N and ethyl bromoacetate (0.92 mL, 8.3 mmol) were added dropwise. After stirring for 8 hours, 50 mL of distilled water and 100 mL of ethylacetate were introduced and stirred to separate layers. The supernatant was washed with 50 Ml of a 1N HCl aqueous solution, 50 mL of a saturated $NaHCO_3$ aqueous solution, and 10 mL of distilled water, and it was dried and concentrated under reduced pressure. The mixture was separated with hexane and ethyl acetate (1 : 1) in a silica gel column, and recrystallized with hexane and ethyl acetate to obtain a white title compound (1.81 g, yield 87%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 1.31(t, J=6.8Hz, 3H), 3.59(s, 3H), 3.63(m, 1H), 3.99(d, J=18.4Hz, 1H), 4.04(m, 1H), 4.25(m, 2H), 4.47(d, J=19.2Hz, 1H), 4.80(dd, J=9.2, 4.0Hz, 1H), 7.47(d, J=8.8Hz, 2H), 7.60(d, J=8.8Hz, 2H), 7.67(d, J=8.0Hz, 2H), 7.90(d, J=8.4Hz, 2H)

Example 31: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-octyl-5-oxo-piperazine-2-carboxylate

The compound of Example 29 (2.13 g, 4.25 mmol) was suspended in 40 mL of dichloromethane, and then Et_3N (0.83 mL, 5.9 mmol) and methane sulfonyl chloride (0.43 mL, 5.52 mmol) were added dropwise while maintaining the temperature at 0 ℃. After stirring at room temperature for 4 hours, the temperature was lowered to 0 ℃, and 20 mL of dichloromethane in which Et_3N (1.2 mL, 8.5 mmol) and octylamine (2.1 mL, 12.7 mmol) were dissolved were added. After stirring at room temperature for 16 hours, the reactant was washed with distilled water, 2N HCl, and a saturated $NaHCO_3$ aqueous solution, and then it was dried and concentrated under reduced pressure. The mixture was separated with ethyl acetate/hexane (4:1) in a silica gel column, and recrystallized with hexane and ethyl acetate to obtain a white title compound (1.35 g, yield 56%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.86(t, J=6.9Hz, 3H), 1.23(m, 12H), 1.40(m, 2H), 3.21(m, 1H), 3.42(m, 1H), 3.53(s, 3H), 3.68(dd, J=12.6, 2.1Hz, 1H), 3.76(dd, J=12.4, 4.4Hz, 1H), 3.93(d, J=16.8Hz, 1H), 4.23(d, J=16.8Hz, 1H), 4.90(m, 1H), 7.47(d, J=8.1Hz, 2H), 7.62(d, J=8.3Hz, 2H), 7.70(d, J=8.3Hz, 2H), 7.86(d, J=8.3Hz, 2H)

Example 32: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-4-octyl-5-oxo-piperazine-2- hydroxamate

To the compound of Example 29 (0.51 g, 0.9 mmol), 6 mL of a 1.7 M H_2NOH solution (prepared from hydroxylamine and KOH according to Fieser and Fieser, Vol. 1, p 478 method) were added and stirred for 3 hours. After 5 hours, the reactant was acidified with a 2N HCl aqueous solution and made pH neutral with a saturated $NaHCO_3$ aqueous solution, and then it was extracted with ethyl acetate, and dried and concentrated under reduced pressure. It was recrystallized with THF/hexane to obtain a white solid title compound (0.12 g, yield 24%).

^1H NMR (DMSO-d_6, 400MHz) δ 0.79(t, J=7.3Hz, 3H), 0.93-1.17(m, 12H), 3.23-3.29(m, 2H), 3.38(m, 2H), 3.98(m, 2H), 4.38(t, J=4.6Hz, 1H), 7.71(m, 4H), 7.89(m, 4H), 9.04(s, 1H), 10.91(s, 1H) ; ^{13}H NMR (DMSO-d_6, 100MHz) δ 14.35, 22.41, 26.42, 26.81, 28.98, 29.07, 31.62, 45.97, 47.22, 47.31, 53.19, 122.78, 127.83, 128.47, 129.53, 132.44, 136.90, 137.66, 143.81, 164.41, 165.04

Example 33: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-4-octyl-5-oxo-piperazine-2-carboxylic acid

The compound of Example 29 (0.45 g, 0.79 mmol) was dissolved in 7 mL of THF, and 1.2 mL of 2N NaOH were added dropwise at 0 ℃. After stirring room temperature for 3 hours, the reactant was concentrated under reduced pressure, acidified with a 2 N HCl aqueous solution, and then extracted with ethyl acetate, and dried and concentrated under

reduced pressure. It was recrystallized with hexane and ethyl acetate to obtain a white title compound (0.34 g, yield 77%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.86(t, J=6.9Hz, 3H), 1.20(br s, 10H), 1.38(m, 2H), 3.16(m, 1H), 3.37(m, 1H), 3.65(dd, J=12.4, 2.0Hz, 1H), 3.70(dd, J=12.7, 4.4Hz, 1H), 3.95(d, J=17.1Hz, 1H), 4.17(d, J=17.3Hz, 1H), 4.34(br, 1H), 4.85(s, 1H), 7.46(d, J=8.6Hz, 2H), 7.59(d, J=8.6Hz, 2H), 7.67(d, J=8.6Hz, 2H), 7.84(d, J=8.5Hz, 2H) ; ^{13}H NMR (CDCl3, 100MHz) δ 14.06, 22.58, 26.62, 29.16, 31.73, 45.74, 47.51, 48.06, 48.50, 53.53, 123.15, 127.52, 127.56, 127.58, 128.12, 128.86, 132.25, 136.87, 137.88, 170.41

Example 34: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-5-oxo-4-prop-2-ynyl-piperazine-2-carboxylate

Title compound was prepared by the same method as in Example 31, except propargyl amine was used as the primary amine.

Example 35: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-5-oxo-4-prop-2-ynyl-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 34 was used.

Example 36: Synthesis of Methyl 4-benzyl-1-(4'-bromo-biphenyl-4-sulfonyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except benzylamine was used as the primary amine.

Example 37: Synthesis of 4-Benzyl-1-(4'-bromo-biphenyl-4-sulfonyl)-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 36 was used.

Example 38: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-dodecyl-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except dodecylamine was used as the primary amine.

Example 39: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-4-dodecyl-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 38 was used.

Example 40: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-(3-butoxy-propyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except 3-butoxypropylamine was used as the primary amine.

Example 41: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-4-(3-butoxy-propyl)-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 40 was used.

Example 42: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-(3-dimethylamino-propyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except 3-(dimethylamino)propylamine was used as the primary amine.

Example 43: Synthesis of 1- (4'-Bromo-biphenyl-4-sulfonyl)-4-(3-

dimethylamino-propyl)-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 42 was used.

Example 44: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-hexyl-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except hexylamine was used as the primary amine. m.p. 127-129 ℃

Example 45: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-4-hexyl-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 44 was used.

Example 46: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-decyl-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except decylamine was used as the primary amine. m.p. 117-118 ℃

Example 47: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-4-decyl-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 46 was used.

Example 48: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-butyl-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31,

except butylamine was used as the primary amine. m.p. 113-115 ℃

Example 49: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-4-butyl-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 38 was used.

Example 50: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-(6-hydroxy-hexyl)-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except 6-amino-1-hexanol was used as the primary amine.

Example 51: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)-4-(6-hydroxy-hexyl)-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 50 was used.

Example 52: Synthesis of Methyl 1-(4'-bromo-biphenyl-4-sulfonyl)-4-octadec-9-enyl-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except oleylamine was used as the primary amine. m.p. 108 ℃

Example 53: Synthesis of 1-(4'-Bromo-biphenyl-4-sulfonyl)- 4-octadec-9-enyl-5-oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except the compound of Example 52 was used.

Example 54: Synthesis of 1-(4'-Methoxy-biphenyl-4-sulfonyl)-4-octyl-5-

oxo-piperazine-2-carboxylic acid

A title compound was prepared by the same method as in Example 33, except 3-methoxybiphenylsulfonyl chloride was used instead of 4-bromobiphenylsulfonyl chloride.

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.87(t, J=6.8Hz, 3H), 1.20(br s, 10H), 1.46(t, J=6.6Hz, 2H), 3.21(m, 1H), 3.44(m, 1H), 3.68(d, J=3.2Hz, 2H), 3.88(s, 3H), 4.13(d, J=17.6Hz, 1H), 4.32(d, J=17.4Hz, 1H), 4.91(t, J=3.1Hz, 1H), 7.03(d, J=8.5Hz, 1H), 7.35(d, J=7.3Hz, 2H), 7.43(d, J=7.9Hz, 2H), 7.73(dd, J=8.5, 2.2Hz, 1H), 8.14(d, J=2.2Hz, 1H); ^{13}H NMR ($CDCl_3$, 100MHz) δ 14.07, 22.62, 26.71, 29.17, 31.76, 46.19, 47.56, 48.59, 53.63, 56.24, 112.77, 126.77, 127.12, 127.65, 129.01, 129.45, 133.40, 133.83, 156.11, 165.11, 170.93

Example 55: Synthesis of Methyl 2-[ethoxycarbonylmethyl-(4-nitro-benzenesulfonyl)-amino]-3-hydroxy-propionate

Methyl 3-hydroxy-2-(4-nitro-benzenesulfonylamino)-propionate (4.0 g, 13.1 mmol) and potassium carbonate anhydride (5.45 g, 39.4 mmol) were suspended in DMF (25 mL), and ethyl bromoacetate (2.91 mL, 26.3 mmol) was added dropwise at 0 ℃. After stirring for 4 hours, 50 mL of distilled water and 100 mL of acetate were introduced and stirred to separate layers. The supernatant was washed with 50 mL of a 5% $Na_2S_2O_3$ aqueous solution, 50 mL of a 1N HCl aqueous solution, 50 mL of a saturated $NaHCO_3$ aqueous solution, and 100 mL of distilled water, and it was dried and concentrated under reduced pressure. The mixture was separated with hexane and ethylacetate (2:1) in a silica gel column to obtain a yellow oil (4.43 g, 86.5).

^{1}H NMR ($CDCl_3$, 400MHz) δ 1.30(t, J=7.1Hz, 3H), 3.63(m, 1H), 3.64(s, 3H), 3.92(dd, J=10.7, 3.4Hz, 1H), 3.98(d, J=19.0Hz, 1H), 4.02(dd, J=10.9, 3.9Hz, 1H), 4.24(m, 2H), 4.45(d, J=19.0Hz, 1H), 4.80(dd, J=9.3, 4.2Hz, 1H), 8.03(d, J=8.8Hz, 2H), 8.35(d, J=8.8Hz, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 14.0, 46.4, 52.7, 60.3, 62.5, 62.6, 124.2, 128.9, 144.7, 150.6, 168.7, 171.6

Example 56: Synthesis of Methyl 1-(4-nitro-benzenesulfonyl)-4-octyl-5-oxo-piperazine-2-carboxylate

A title compound was prepared by the same method as in Example 31, except that octylamine as the primary amine and the compound of Example 55 were used to obtain a white solid title compound (yield 88%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.86(t, J=6.9Hz, 3H), 1.24(m, 10H), 1.43(m, 2H), 3.22(m, 1H), 3.44(m, 1H), 3.57(s, 3H), 3.72(d, J=12.7Hz, 1H), 3.80(dd, J=12.7, 4.2Hz, 1H), 3.86(d, J=16.6Hz, 1H), 4.26(d, J=16.6Hz, 1H), 4.91(m, 1H), 7.98(d, J=8.8Hz, 2H), 8.36(d, J=8.8Hz, 2H); m.p. 85-86 ℃

Example 57: Synthesis of Methyl 4-octyl-5-oxo-1-(4-pyrrol-1-yl-benzenesulfonyl)-piperazine-2-carboxylate

The compound of Example 56 (0.69 g, 1.5 mmol) was put in 10 mL of a MeOH solution to which $SnCl_2 \cdot 2H_2O$ (1.37 g, 6.4 mmol) was added, and stirred for 1.5 hours while maintaining the temperature at 50 ℃. A saturated $NaHCO_3$ aqueous solution was introduced and stirred for 2 hours, and then it was extracted with ethyl acetate. After distillation under reduced pressure, 2,5-dimethoxytetrahydrofuran (0.20 mLo, 1.5 mmol) and 1 mL of acetic acid were introduced and refluxed for 2 hours. 50 mL of ethyl acetate was

introduced and the reactant was washed with 50 mL of a saturated $NaHCO_3$ aqueous solution and 50 mL of a 1N HCl aqueous solution, and dried and then concentrated under reduced pressure. The mixture was separated with hexane and ethyl acetate (3:1) in a silica gel column to obtain a yellow oily title compound (0.19 g, 26%).

^1H NMR ($CDCl_3$, 400MHz) δ 0.86(t, J=6.8Hz, 3H), 1.25(m, 10H), 1.39(m, 2H), 3.20(m, 1H), 3.43(m, 1H), 3.55(s, 3H), 3.74(m, 2H), 3.91(d, J=16.6Hz, 1H), 4.22(d, J=16.8Hz, 1H), 4.89(m, 1H), 6.41(t, J=2.4Hz, 2H), 7.16(t, J=2.4Hz, 2H), 7.52(d, J=8.8Hz, 2H), 8.85(d, J=8.8Hz, 2H)

Example 58: Synthesis of 4-Octyl-5-oxo-1-(4-pyrrol-1-yl-benzenesulfonyl)-piperazine-2-carboxylic acid

The compound of Example 57 (0.19 g, 0.4 mmol) was dissolved in 5 mL of THF, and 1 mL of 2N NaOH was added dropwise at 0 ℃. After reaction at room temperature for 3 hours, the reactant was concentrated under reduced pressure and acidified with a 2N HCl aqueous solution, extracted with ethyl acetate, and concentrated under reduced pressure. It was then recrystallized with hexane and ethyl acetate to obtain an ivory colored compound (0.07 g, yield 28%).

^1H NMR ($CDCl_3$, 400MHz) δ 0.79(br, 3H), 1.07-1.15(m, 14H), 3.42(m, 1H), 3.74(m, 3H), 3.90(br, 1H), 4.23(br, 1H), 4.64(br, 1H), 6.34(s, 2H), 7.07(s, 2H), 7.40(br, 2H), 7.86(br, 2H)

Example 59: Synthesis of Methyl 1-[4-(4-chloro-benzoylamino)-benzenesulfonyl]-4-octyl-5-oxo--piperazine-2-carboxylate

The compound of Example 56 (0.55 g, 1.2 mmol) was put into 10 mL of a MeOH solution to which $SnCl_2 \cdot 2H_2O$ (1.1 g, 4.8 mmol) was added, and stirred for 1 hour while maintaining the temperature at 50 ℃. A saturated $NaHCO_3$ aqueous solution was introduced and the mixture was stirred for 1 hour, and then it was extracted with ethyl acetate. After distillation under reduced pressure and vacuum drying, the mixture was dissolved in 20 mL of dichloromethane and Et_3N (0.41 mL, 2.9 mmol), and 4-chlorobenzoyl chloride (0.31 mL, 2.4 mmol) was added while maintaining the temperature at 0 ℃. After reaction for 6 hours, the reactant was washed with a saturated NaHCO3 aqueous solution and a 1N HCl aqueous solution, and dried and concentrated under reduced pressure. It was then recrystallized with hexane and ethyl acetate to obtain a white solid (0.62 g, 91%).

^1H NMR ($CDCl_3$, 400MHz) δ 0.86(t, J=6.8Hz, 3H), 1.27(m, 10H), 1.41(m, 2H), 3.20(m, 1H), 3.42(m, 1H), 3.56(s, 3H), 3.65(dd, J=12.7, 2.0Hz, 1H), 3.75(dd, J=12.4, 4.4Hz, 1H), 3.90(d, J=16.6Hz, 1H), 4.17(d, J=16.6Hz, 1H), 4.87(m, 1H), 7.48(d, J=8.5Hz, 2H), 7.77(d, J=9.0Hz, 2H), 7.84(d, J=8.8Hz, 2H), 7.86(d, J=8.5Hz, 2H), 8.33(s, 1H) ; m.p. 171-173 ℃

Example 60: Synthesis of 1-[4-(4-chloro-benzoylamino)-benzenesulfonyl]-4-octyl-5-oxo-piperazine-2-carboxylic acid

The compound of Example 59 (0.56 g, 0.99 mmol) was dissolved in 8 mL of THF, and 2 mL of 2N NaOH were added dropwise while maintaining the temperature at 0 ℃. After stirring at room temperature for 2 hours, 20 mL of distilled water were added and a 2N HCl solution was further added to

control the pH to 1-2, and then the reactant was extracted with ethyl acetate. The supernatant was collected, and dried and concentrated under reduced pressure, and then recrystallized with ethyl acetate/hexane to obtain a light yellow solid compound (0.15 g, yield 27%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 0.86(t, J=6.8Hz, 3H), 1.23(m, 10H), 1.43(m, 2H), 3.32(m, 2H), 3.65(d, J=12.2Hz, 1H), 3.78(m, 2H), 4.05(d, J=16.8Hz, 1H), 4.84(s, 1H), 7.48(d, J=8.3Hz, 2H), 7.53(d, J=8.3Hz, 2H), 7.64(d, J=8.5Hz, 2H), 7.93(d, J=8.3Hz, 2H), 9.22(s, 1H) ; m.p. 151-154 ℃

[Experiment Example]

Experiment 1: Measurement of MMP inhibiting activities

Inhibitory activities of all the enzymes were measured similarly to the MMP-2 activity measuring method shown below. Prior to measuring, proMMP-2 was treated with 1mM p-aminophenyl mercuricacetate at 37 ℃ for 45 minutes to activate it. The ProMMP-9 was activated to an enzyme with MMP-3, and stored at –80 ℃ until used.

MMP activities were measured by fluorescence assay by changing a microtiter plate formate according to the reported method (Knight, C. G., Willenbrock, F., Murphy, G. A., FEBS Lett. 1992, 296, 263-266). On a dynatech MicroFLUOR plate, a buffer solution comprising 50 Mm Tris-HCl pH 7.5, 10 mM $CaCl_2$, 0.15 M NaCl, 0.05% Brij, and 1-8 μM of a substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2), and various concentrations of inhibitors were introduced, and it was reacted with activated enzymes at 37 ℃ for 20-30 minutes. Reaction was terminated by putting the reactant in 50 mM

EDTA, and then fluorescence was measured with a spectrofluorometer attached to a microplate reader (λex 328 nm, λ em 393 nm). The inhibiting activity degree was indicated by an IC_{50} value, which is a concentration inhibiting activity by 50% compared to the control. Results were as shown in Table 1.

[Table 1]

Enzyme inhibiting constant

	IC_{50} (μM)				
	MMP-1	MMP-2	MMP-9	MMP-13	MMP-14
Example 5		0.004	0.0124		0.028
Example 7	0.052	0.007	0.025	0.018	0.036
Example 15	>10	>10		>10	
Example 19	0.047	0.015		0.014	
Example 25	0.082	0.003		0.016	
Example 32	0.016	0.002	0.0013	0.007	
Example 33	2.430	0.080		2.100	
Example 39	8.270	0.567		2.350	
Example 45	0.095	0.011		0.082	
Example 47	5.400	0.140		2.460	
Example 49	0.114	0.009		1.130	
Example 51	0.029	0.005		0.019	
Example 53	>10	0.220		>10	
Example 60	0.018	0.003	0.0032	0.024	

As shown in Table 1, the compound of the present invention is superior as a proteinase inhibitor.

Experiment 2: Measurement of tube formation activity

In a culture flask previously coated with gelatin, HUVEC (human umbilical vein endothelial cell) cells cultured with a M199 medium (containing 20% FBS, 3 ng/ml bFGF, 100 μ g/ml heparin) were treated with trypsin/EDTA, and then number of cells are counted so that number of cells may be $2x10^4$ cells/well in a 96-well plate previously coated with matrigel. Samples were then added and cultured in a CO_2 culture medium at 37 ℃ for 16-24 hours. After cultivation, whether or not endothelial cells were differentiated into capillary tubes was observed with a microscope, and activities were judged on the following basis. Results were as shown in Table 2.

- : control
+/- : tube almost resembles control
+ : inhibition
++ : significant inhibition
+++ : complete inhibition

[Table 2]

	Tube Formation (concentration, μM)			
	100	50	5	0.5
Control	-	-	-	-
Example 5	++	+	+/-	
Example 7		+	+/-	
Example 9		+/-	-	
Example 11		+	+/-	
Example 13	+	+	+/-	
Example 15	++	+	+	
Example 17	++	+	+	
Example 19	++	+	+	
Example 21		+	+/-	

Example 23	+++	++	+	
Example 25	+	-	-	
Example 26	++	+	+/-	
Example 27		++	++	
Example 32	+++	+++	++	
Example 33	+++	++	+	
Example 35		+++	++	++
Example 37		+++	++	++
Example 39		+	-	-
Example 41		+++	++	++
Example 43		++	++	+
Example 45		++	++	++
Example 47		+++	++	++
Example 49		++	++	+/-
Example 58		++	++	+/-
Example 60		++	++	+

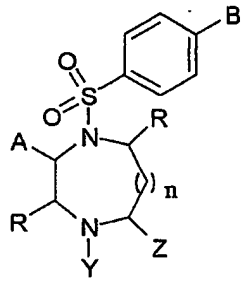
As shown in the above Table 2, the compounds of Examples 5 to 60 according to the present invention have superior angiogenesis inhibiting activities compared to the control. Therefore, the compound of the Chemical Formula 1 of the present invention can inhibit matrix metalloproteinase activity to efficiently control angiogenesis.

As explained, the compound of the Chemical Formula 1 of the present invention acts as a superior matrix metalloproteinase inhibitor and can be useful for a treating agent of various diseases related to angiogenesis such as cancer, periodontal disease, arthritis, etc., and it is particularly very effective for an anticancer drug capable of treating and preventing cancer.

WHAT IS CLAIMED IS:

1. A compound represented by the following Chemical Formula 1, optical isomers, pharmaceutically acceptable salts, or solvates thereof:

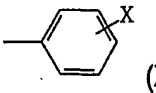
[Chemical Formula 1]



wherein,

n is 0, 1, 2, or 3;

A is CO_2H, CONHOH, CH_2SH, or CH_2OH;

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is

hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl group, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound;

R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound;

Z is hydrogen, oxygen, or sulfur, provided that in the case Z is oxygen or sulfur it takes a double bond;

Y is hydrogen; a C1-18 alkyl group; an aryl group; a heteroaryl; C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound; a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; a urea compound of NHCONHR; a C1-8 lower alkyl group having a double bond or a triple bond; or a C9-20 higher alkyl group having a double bond or a triple bond (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C-18 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-9 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound.

2. The compound according to Claim 1, wherein A is CONHOH.

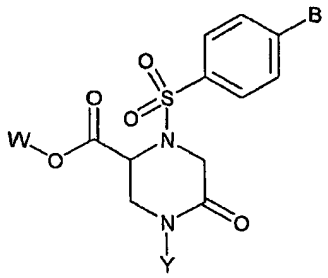
3. The compound according to Claim 1, wherein A is CO_2H.

4. The compound according to Claim 1, wherein A is CH_2OH.

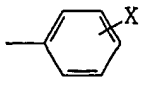
5. The compound according to Claim 1, wherein A is CH_2SH.

6. A process for preparing a compound of Claim 2, comprising the step of reacting a compound of the following Chemical Formula 2 with NH_2OH and KOH, or NH_2OH in the presence of $AlCl_3$:

[Chemical Formula 2]



wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group; 

(X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative,

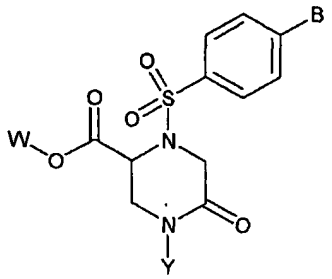
an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound;

W is hydrogen, or a methyl, ethyl, t-butyl, or C1-8 lower alkyl group comprising a benzyl group;

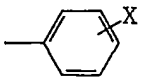
Y is hydrogen; a C1-18 alkyl group; an aryl group; a heteroaryl; a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound; a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; a urea compound of NHCONHR; a C1-9 lower alkyl group having a double bond or a triple bond; or a C9-20 higher alkyl group having a double bond or a triple bond (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound).

7. A process for preparing a compound of Claim 3, comprising the step of hydrogenating a compound of the following Chemical Formula 2 in the presence of an inorganic base, an acid-base, or a Pd/C catalyst:

[Chemical Formula 2]



wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound;

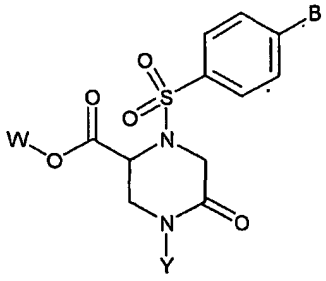
W is hydrogen, or a methyl, ethyl, t-butyl, or C1-8 lower alkyl

group comprising a benzyl group;

Y is hydrogen; a C1-18 alkyl group; an aryl group; a heteroaryl; a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound; a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; a urea compound of NHCONHR; a C1-9 lower alkyl group having a double bond or a triple bond; or a C9-20 higher alkyl group having a double bond or a triple bond (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound).

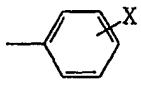
8. A process for preparing a compound of Claim 3, comprising the step of converting the ester group of a compound of the following Chemical Formula 2 into alcohol with a reductant comprising $NaBH_4$ in the presence of a solvent:

[Chemical Formula 2]



wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a

heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound;

W is hydrogen, or a methyl, ethyl, t-butyl, or C1-8 lower alkyl group comprising a benzyl group;

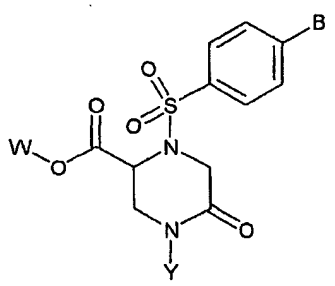
Y is hydrogen; a C1-18 alkyl group; an aryl group; a heteroaryl; a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound; a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; a urea compound of NHCONHR; a C1-9 lower alkyl group having a double bond or a triple bond; or a C9-20 higher alkyl group

having a double bond or a triple bond (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound).

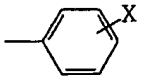
9. A process for preparing a compound of Claim 4, comprising the step of Mitsunobu-reacting a compound of Claim 3 and adding NaOH.

10. A compound represented by the following Chemical Formula 2, optical isomers, pharmaceutically acceptable salts, or solvates thereof:

[Chemical Formula 2]



wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group; 

(X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N- heteroaryl group, an S-aryl group, an

S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound;

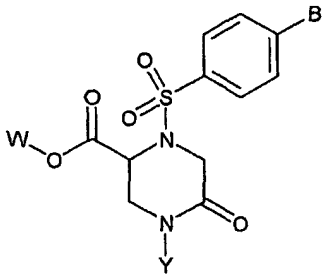
W is hydrogen, or a methyl, ethyl, t-butyl, or C1-8 lower alkyl group comprising a benzyl group;

Y is hydrogen; a C1-18 alkyl group; an aryl group; a heteroaryl; a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound; a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; a urea compound of NHCONHR; a C1-9 lower alkyl group having a double bond or a triple bond; or a C9-20 higher alkyl group having a double bond or a triple bond (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound).

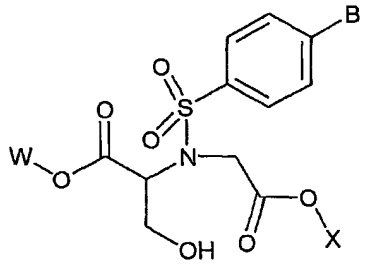
11. A process for preparing a compound of the following Chemical Formula 2, comprising the step of reacting a compound of the following

Chemical Formula 3 with methanesulfonyl chloride, toluenesulfonyl chloride, or triflic anhydride in the presence of a base, and reacting it with a primary amine:

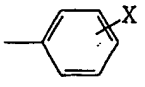
[Chemical Formula 2]



[Chemical Formula 3]



wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond or a triple bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl

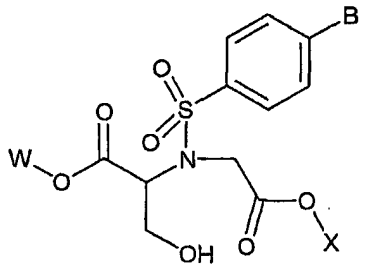
group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound;

W and X are independently or simultaneously hydrogen, or a methyl, ethyl, t-butyl, or C1-8 lower alkyl group comprising a benzyl group;

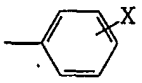
Y is hydrogen; a C1-18 alkyl group; an aryl group; a heteroaryl; a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound; a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; a urea compound of NHCONHR; a C1-9 lower alkyl group having a double bond or a triple bond; or a C9-20 higher alkyl group having a double bond or a triple bond (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound).

12. A compound represented by the following Chemical Formula 3, optical isomers, pharmaceutically acceptable salts, or solvates thereof:

[Chemical Formula 3]



wherein,

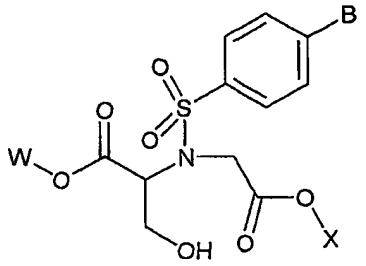
B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20 higher alkyl group comprising a double bond or a triple bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; and

W and X are independently or simultaneously hydrogen, or a methyl,

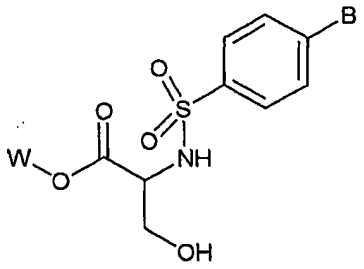
ethyl, t-butyl, or C1-8 lower alkyl group comprising a benzyl group.

13. A process for preparing a compound represented by the following Chemical Formula 3, comprising the step of reacting a compound of the following Chemical Formula 4 with ethyl bromoacetate and a halogen compound, in the presence of an inorganic base and DMF or acetonitrile solvent:

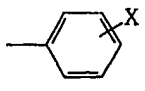
[Chemical Formula 3]



[Chemical Formula 4]



wherein,

B is hydrogen; a C1-8 lower alkyl group; a nitro group; an aryl group; a heteroaryl group; a pyrrole group; a halogen atom; a C1-8 O-lower alkyl group; an O-aryl group; an N-lower alkyl group; an S-lower alkyl group;  (X is hydrogen, a C1-8 lower alkyl group, a C9-20 higher alkyl group, a C9-20

higher alkyl group comprising a double bond or a triple bond, an aryl group, a heteroaryl group, a halogen atom, an O-lower alkyl group, an O-aryl group, an O-heteroaryl group, an N-aryl group, an N-heteroaryl group, an S-aryl group, an S-heteroaryl group, a C1-20 alkyl-amine derivative, a C1-20 alkyl-carboxylic acid derivative, an amine group, or a nitro group.); an amide compound of CONHR or NHCOR; a carbamate compound of NHCOOR; or a urea compound of NHCONHR (R is hydrogen, a C1-8 lower alkyl group, an aryl group, a heteroaryl, a tetragonal to octagonal cyclic compound, a C1-8 lower alkyl group substituted by a tetragonal to octagonal cyclic compound, a tetragonal to octagonal heterocyclic compound, or a C1-8 lower alkyl group substituted by a tetragonal to octagonal heterocyclic compound; and

W and X are independently or simultaneously hydrogen, or a methyl, ethyl, t-butyl, or C1-8 lower alkyl group comprising a benzyl group.

14. A pharmaceutical composition comprising a compound of the Chemical Formula 1 of Claim 1, an optical isomer, a pharmaceutically acceptable salt, or a solvate thereof, as an active ingredient.

15. A method for treating cancer metastasis and solid cancer using the pharmaceutical composition of Claim 14.

16. A method for treating diseases related to angiogenesis using the pharmaceutical composition of Claim 14.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR02/00759

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7: C07D 403/12, C07D 211/96, C07D 241/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and application for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, NPS, PAJ, CA on line, STN on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9633172 A (PFIZER INC.) 24 OCT 1996 claims 1-5	1-3, 14-16
X X	US 5753653 (AGOURON PHARMACEUTICALS INC.) 19 MAY 1996 claims 1-9, 15-17 page 26; example 3	1, 2, 10, 14-16 3
X	WO 0102371 A (NIPPON SODA CO., LTD.) 11 JAN 2001 claim 1	1, 4
Y	WO 9827069 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 25 JUN 1998 page 3; process 3	6
Y	J. MED. CHEM., vol. 43, no. 3, pp. 369-380 (2000) page 370; scheme 1	6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevence
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 AUGUST 2002 (07.08.2002)	12 AUGUST 2002 (12.08.2002)
Name and mailing address of the ISA/KR Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-3556	Authorized officer BAIK, Kyong UP Telephone No. 82-42-481-5600

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR02/00759

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9633172 A	24. 10. 96	ZA 9603130 A	20. 10. 97
		US 5861510	19. 01. 99
		TW 0418197 B	11. 01. 01
		TR 0960966 A	21. 11. 96
		SG 0043350 A	17. 10. 97
		RU 2146671 C	20. 03. 00
		PT 0821671 T	30. 04. 01
		NZ 0286417 A	26. 06. 98
		NO 0961585 A	21. 10. 96
		NO 0306253 B	11. 10. 99
		KR 0219976 B	01. 09. 99
		JP 10507466 T	21. 07. 98
		JP 3053222 B	19. 06. 00
		IL 0117868 A	04. 08. 96
		FI 0873974 A	16. 10. 97
		ES 2153031 T	16. 02. 01
		EP 0821671 B	27. 12. 00
		EP 0821671 A	04. 02. 98
		DK 0821671 T	23. 04. 01
		DE 69519751 T	19. 04. 01
		CZ 0287551 B	13. 12. 00
		CN 1304930 A	25. 07. 01
		CA 2218503 A	24. 10. 96
		BR 9602001 A	07. 04. 98
		AU 5080296 A	31. 10. 96
		AU 0694635 B	23. 07. 98
		AT 0198326 E	15. 01. 01
US 5753653	19.05.98	WO 9720824 A	12. 06. 97
		US 6153757	28. 11. 00
		TR 9800990 T	21. 07. 98
		SK 0073898 A	11. 01. 99
		PL 0327275 A	07. 12. 98
		NZ 0325559 A	28. 01. 00
		NO 0311360 B	19. 11. 01
		JP 0502330 T	29. 02. 00
		IL 0124559 A	06. 12. 98
		HU 9902092 AB	28. 09. 99
		EP 1095936 A	02. 05. 01
		CZ 9801733 A	11. 11. 98
		CN 1207734 A	10. 02. 99
		CA 2238306 AA	12. 06. 97
		BR 9611929 A	18. 05. 99
		BG 0102510 A	31. 08. 99
		AU 0725831 B	19. 10. 00
		AP 21002270 A	30. 09. 01

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR02/00759

WO 0102371 A	11. 01. 01	JP 2000007664 A	11. 01. 00
WO 9827069 A	25. 06. 98	ZA 9711284 A	23. 06. 98
		US 6333324 B	25. 12. 01
		JP 1506257 T	15. 05. 01
		EP 0948489 A	13. 10. 99
		AU 5412298 A	15. 07. 98